



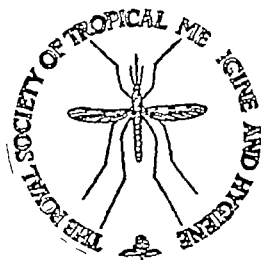
# TRANSACTIONS

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## ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

PATRON

HIS MAJESTY THE KING.



ZONAE TORRIDAE TUTAMEN

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TRANSACTIONS  
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ROYAL SOCIETY OF TROPICAL MEDICINE  
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VOL. XXXVII No 1 JULY 1943

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COMMUNICATIONS

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LYSO LECITHIN FRAGILITY IN BLACKWATER FEVER AND  
HAEMOLYTIC JAUNDICE.

BY

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AND

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In a previous paper (FOY KONDI MOURMIDIS 1941) we showed that red blood cells transfused into a haemolytic case of blackwater fever from three different donors underwent haemolysis just as readily as did the blackwater fever patients' own cells. It was thus established that the red cells in cases of blackwater fever are not more liable to destruction than are cells from normal individuals. This has been interpreted as implying that it is not the

red cells themselves that are at fault in blackwater fever but that there is some circulating haemolysis that destroys all red cells that come into contact with it, irrespective of their origin.

No satisfactory explanation has so far been given of the nature of this haemolysin or from whence it arises with such suddenness to cause the catastrophic haemolysis that occurs in blackwater fever. Nor has any answer been given to the question whether the haemolysis that occurs in such conditions as acholuric jaundice, favism, and the haemolytic splenic anaemias is of the same origin and nature as that of blackwater fever. We know that in some of these conditions the red cells themselves are not normal as is shown by their increased fragility to saline but in others so far as is known, the red cells appear to be normal. In blackwater fever malaria no doubt plays an important role which it does not in the others.

Attempts to link up these various forms of haemolysis have been made by a number of different workers at various times among which that of BERGQUHIST and FAHRBAUM (1936) and FAHRBAUM (1939) is perhaps the most attractive. Briefly put, these workers have postulated the production of a haemolytic substance lyso-lectihin, in the stagnating blood of the enlarged spleen, which acts on the surface of the red cells so as either to haemolyse them or predispose them to destruction. A prerequisite for the production of lyso-lectihin is the separation of the plasma and cells such as would occur in the spleen especially if this organ is enlarged. The work of KNISELY (1936) on the anatomy of the spleen and the blood circulation therein is a considerable prop to this hypothesis of FAHRBAUM. It should however be pointed out that more recent work by MACKENZIE and his collaborators (1940) and WHIPPLE (1941) on the splenic circulation have led them to draw quite opposite conclusions regarding blood distribution in this organ.

So far as we are aware no attempt has been made to investigate the kinetics of lyso-lectihin haemolysis on the lines laid down by PONDER (1934) and accurate quantitative studies of the process are entirely lacking. SINGER (1940 & 1941), SINGER and MILLER (1941) and a number of others have carried out roughly quantitative fragility tests using varying dilutions of lyso-lectihin in saline with washed red cells taken into white-cell-counting pipettes. After allowing the mixture in the pipettes to stand for 1 hour the unhaemolysed cells remaining in the pipette are counted in an ordinary counting chamber and the percentage haemolysis estimated. PONDER and others have shown that this method of estimating haemolysis is unsatisfactory especially where the haemolysis is rapid as it is in the case of lyso-lectihin if only for the reason that as much as  $\frac{1}{2}$  to 1 hour may elapse between making the count on the first pipette and the last. Further the sedimentation that occurs while the pipettes are incubating introduces another unknown factor into the system, since it is probable that the lyain acts through surface phenomena. We have therefore in our work on lyso-lectihin haemolysis used the method recommended by PONDER

with a Pulfrich photometer modified to meet the needs of our special investigation. By this method not only is the lyso-lecithin red-cell system kept from sedimenting, but the degree of haemolysis occurring in all the tubes can be read within a few minutes of one another and with accuracy that cannot be approached with the pipette method.

Using this method we have estimated the lyso-lecithin fragility of cells from cases of blackwater fever controlled against normal cells, and compared with saline fragility.

In some quarters the assumption has been made that lyso-lecithin and saline fragility follow one another in a general way but from the work outlined below it is clear that this is not so and it seems that saline and lyso-lecithin form two different resistance series (RYWOSCH 1911, PONDER 1934) in the same sense as do saponin and saline. The cells of acholuric jaundice by contrast show an increased fragility to both saline and lyso-lecithin, those of blackwater fever showing it only to lyso-lecithin.

#### *Case Details and Investigations*

A child aged 13 years spent some weeks in a malarious area in Natal returned to Johannesburg and developed a fever which was clinically diagnosed as malaria and the patient given 30 x 0.1 grammes of atebri. Although no previous history of malaria was obtainable the child had in a previous year spent some time in the game reserve which is notoriously malarious. About 38 hours after his last dose of atebri he passed a quantity of black urine containing 290 mg per cent. of oxyhaemoglobin and 280 mg per cent. of methaemoglobin with a pH of 8.2. His spleen was 1 (Hackett) and his skin was deeply tinged with yellow partly no doubt from atebri and partly from jaundice. No quinine was given at any time. The following day 11.11.42 he was still passing black urine containing 120 mg per cent. of oxyhaemoglobin and 238 mg per cent. methaemoglobin with a pH of 6.8. Blood examination on this day 11.11.42 gave the following results—

R.B.C.	2,260,000 per c.mm. $\pm$ 3 per cent.	Indirect haemobilirubin	2.5 mg per cent.
W.B.C.	14,000 per c.mm.	Methaemalbumin	238 mg per cent.
Haematocrit	20 per cent.	Oxyhaemoglobin	29 mg per cent.
Crude M.C.V.	83 $\mu^3$	Parasites	Negative and no pigment.
Reticulocytes	9.5 per cent.		

On 12.11.42 his urine was almost clear and contained 56 mg. per cent. oxyhaemoglobin and 280 mg per cent. methaemoglobin with a pH of 6.5. Thereafter the urine cleared completely and the patient made an uneventful recovery.

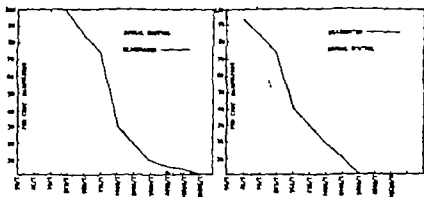
Blood taken on 14.11.42 gave the following results—

R.B.C.	2,270,000 per c.mm. $\pm$ 3 per cent.	Methaemalbumin	48.0 mg per cent.
Haematocrit	21 per cent.	Oxyhaemoglobin	9.5 mg per cent.
Crude M.C.V.	82 $\mu^3$	Parasites	Negative
Indirect bilirubin	1.8 mg per cent.		

Lyso-lecithin fragility tests were done on 11.11.42 and 14.11.42 and the results shown in Tables I and II and Charts 1 and 2. The saline fragility done on the same blood at the same time is shown in Table III and Chart 3. For comparison similar tests were done on a case of haemolytic jaundice and the results given in Table IV and Chart 4. All the tests were done against the same control. Throughout the experiments the pH of the system was determined electrometrically and as will be seen from the tables there was little change the control and the unknown always having the same values. Acid haemolysis such as occurs in paroxysmal nocturnal haemoglobinuria, can therefore be ruled out (HAM and CASTLE 1940). No buffers were added to any of the systems as these have been shown to interfere with the reaction and haemoglobin itself acts as an efficient buffer.

In Charts 5, 6 and 7 Price Jones curves are given showing that there was some change in the diameter of the red cells (see below). Owing to the patient leaving the hospital we were unable to follow up the case after 14.11.42.

In Table V formulæ and figures are given showing the variations in the dimensions of the red cells that take place in blackwater fever haemolytic jaundice and normals. It will be seen from this table that the red cells from blackwater fever seem to occupy a position that is intermediate between that of haemolytic jaundice and normal. Clearly more material is necessary before final conclusions can be drawn, but we think that the data presented here are sufficient to indicate the general trend of events.



1. 50-LECITHIN DILUTIONS

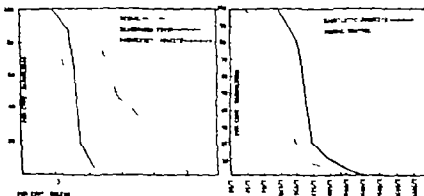
CHART 1

Lyso-lecithin Fragility Blackwater fever (11.11.47)

1. 50-LECITHIN DILUTIONS

CHART 2,

Lyso-lecithin Fragility Blackwater Fever (14.11.42)



50-LECITHIN DILUTIONS

CHART 3

Saline Fragility in Blackwater Haemolytic Jaundice and Normal Control

50-LECITHIN DILUTIONS

CHART 4

Lyso-lecithin Fragility Haemolytic Jaundice (14.11.47)

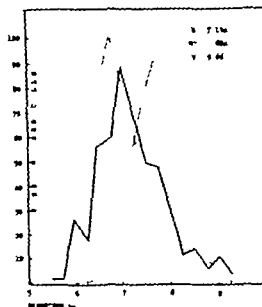


CHART 5

Blackwater Fever (11 11 42)

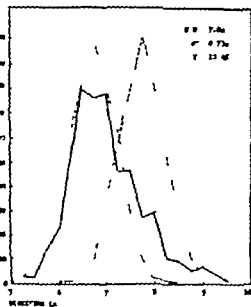


CHART 6

Blackwater Fever (14 11 42)

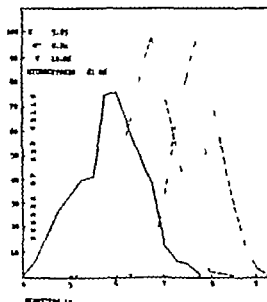


CHART 7

Haemolytic Jaundice (11 11 42)

As has been pointed out by VON BOROS (1926) and more recently by HADEN (1935) the crude mean corpuscular volume (M.C.V.) such as is obtained by dividing the haematocrit percentage by the red cell count gives little real insight into the actual changes in shape of the red cell. It is necessary to bear in mind that both thickness and diameter changes take place concurrently and that the ratio of these changes to one another will give a clearer insight, into the

final shape of the cell than measurements of each dimension separately. It will be seen for example that the crude M.C.V. makes the blackwater fever cells somewhat more spherocytic than normal but when the thickness changes are considered together with the diameter changes as is shown in the corrected M.C.V. then the true state of affairs is evident, and the blackwater fever cells are even more spherocytic than normal, but less so than those of haemolytic jaundice. Similarly with regard to the diameter thickness ratio. Normally the red cell has a diameter which is approximately four times the thickness in haemolytic jaundice this has changed to twice the thickness only in blackwater fever it is about three times.

The lyso-lectithin used in these experiments was prepared either by a modified SINGER method or by the cadmium chloride method of LIVING (1924). Prepared by the latter method it always had a much higher titre than by SINGER's method and was very much less variable.

### DISCUSSION

It is clear from the above experiments that the behaviour of the red cells from blackwater fever and haemolytic jaundice to lyso-lectithin are similar although their saline fragility is so different. SINGER has shown that the red cells from haemolytic jaundice have an increased fragility to lyso-lectithin, and this is confirmed in the present case (Table IV and Chart 4). He considers however that lyso-lectithin is probably not a factor in the haemolysis that occurs in this disease. Commenting on the increased lyso-lectithin fragility of the cells in acholuric jaundice DACIE (1941) suggests that this is due to their having absorbed more lyso-lectithin during their passage through the spleen. It should be mentioned however that their increased fragility to saline can hardly be explained in this way.

A substance that is powerfully haemolytic *in vitro* may have no action when injected *in vivo* even in great amounts. We have found for example that lyso-lectithin which is haemolytic *in vitro* in very high dilutions has no effect whatever when injected in relatively huge amounts intravenously into baboons. We are aware that there are many substances such as serum proteins, that have the power of inhibiting haemolysis (PONDER, 1934. HALLAWAY 1933. HOLDEN 1935).

In all our experiments we have found that, when cells are suspended in normal saline they appear either normal or slightly crenated. When the smallest amount of lyso-lectithin is added to the suspension the cells rapidly become spherocytic. If these spherocytes are carefully watched they will be seen to "swell slowly get fainter and fainter become transparent and then disappear completely. A similar series of events takes place when the cells are suspended in 0.05 per cent cobra venom (*Naja flavus* and *Naja naja*). PONDER (1942) has shown that in many cases these "ghosts" can be made to reappear by suspending them in fresh saline and interprets the phenomena as being due not to reversal in haemolysis but to changes in the permeability of the envelope of the red

cell which permits the haemoglobin to escape into the surrounding fluid. The latter takes on the same colour density as the cells which cannot therefore be seen while resuspending them in fresh saline allows the denser coloured cells to 'show up' in the clearer fluid. According to this view the red cell envelope is not therefore destroyed at once—changes in its permeability allow the contents to escape and rupture of the wall may take place later. Whether a similar series of changes is taking place in blackwater fever and haemolytic jaundice is at the moment not known.

HAM and CASTLE (1940) suggest that the haemolysis occurring in such conditions as acholuric jaundice, icterus gravis neonatorum, and drug poisoning from arsine or sulphonamides, is due to intravascular stasis, which leads to progressive swelling of the erythrocytes, spherocytosis and increased "osmotic" fragility. They believe that these events are due to metabolic changes in the red cell and not to circulating haemolysins. The authors consider that the intravascular stasis which occurs normally in the spleen and other organs is the immediate mechanism in those haemolytic anaemias characterized by increased red cell fragility to saline and they do not believe that lyso-lecithin is a factor in the haemolysis of red cells either *in vitro* or *in vivo*. Their suggestion that 'normal cells' may be destroyed by "abnormal stasis" and 'abnormal cells' by 'normal stasis' is somewhat difficult to prove one way or the other and their experiments with concanavalin A. are interesting but not conclusive. Certainly there is evidence that in many of these haemolytic conditions the red cells become spherocytes and often before there is any sign of anaemia clinically. As can be shown by the formula of VON BOROS (1926) this spherocytosis is accompanied by decreases in diameter-thickness ratio, volumes and areas. Although evidence is presented here to show that similar changes are taking place in blackwater fever, they are not in any way linked to changes in osmotic saline fragility as has been suggested by HAM and CASTLE and HADEN, tending to confirm the view expressed by MOMIGLIANO-LEVI and BAIKATI (1935a & 1935b). The increased fragility to lyso-lecithin is difficult to explain in the present state of our knowledge of the chemistry of the red cell membrane. It seems not unlikely that changes in the dimensions of the cell may bring about differences in the molecular configuration of the envelope that may permit lyso-lecithin to attack the lipo-protein complex therein.

There is no clear explanation why the red cells of certain animals are more susceptible to some haemolysins than to others, nor is there any explanation why the red cells of the same animal differ in their susceptibility to the same haemolysin in different states of health and disease. The purely physical one advanced by HAM and CASTLE would not seem to account for all the facts. ERICKSON and her colleagues (1938) have stated that the amount of lipid present in the cell membrane is closely related to the dimensions of the cell and that the maximum volume that a cell can attain without losing its integrity is a function of lipo-protein ratio in its membrane. HÖRTER (1936) has shown that this critical volume for the sheep is 126, for the ox 130 and for man



146 taking normal in plasma as 100. MEYER (1929) has further shown that films which contain a high protein content can "stretch" more than those with a high lipid and HUNTZEL and PRAKKE (1933) have related this to the lipid content of sheep ox and man cells pointing out that sheep cells have a much higher lipid content than those of either the ox or man.

It should however be pointed out that there is at present little agreement between the analysis figures given by different authors for various membranes. DZIEMIAN (1939), for example considers that there is little correlation between the lipid content of the cell membrane and its permeability to lipid soluble substances no matter how this is expressed which is difficult to harmonize with the views expressed by ERICKSON. DZIEMIAN (1939), BODANSKY (1931-1932, 1933) and JACOBS GLASSMAN and PARFART (1935) consider that the permeability of the cell membrane is dependent upon the length of the carbon atom chain the one increasing as the other. HÖBER has further suggested that the cell membrane is made up of a mosaic of lipid solvent, and non-lipid sieve like areas and that the different effects of haemolysins on red cells is due to varying combinations of these two a view that might fit in with that expressed by ERICKSON. From the work of NORRIS (1939) and PLATTNER and HINTNER (1930), it seems that haemolysins like saponin attack only the lipid part of the red cell membrane and that some sort of envelope still remains after haemolysis. Sodium oleate and taurocholate appear to attack the protein complex (SCHULMAN and RIDGAL, 1937).

WHIPPLE (1941) considers that spherocytes being more rotund than normal red cells (i.e. having no narrow diameter) clog the capillaries of the spleen hold up the cells in this organ and thus subject them for a longer time to the influence of phagocytosis and lyso-lectihin. A question needing discussion is whether the spherocytes by blocking the capillaries cause stress or stress is caused by some unknown factor and produces the spherocytes as HAM and CASTLE suggest. WHIPPLE considers that the process is a vicious circle.

Any changes that the red cells undergo would seem not to be *spso facto* changes but changes produced by the interaction of the cells with the environment that surrounds them. Changes probably take place not only in the cells but also in the medium which bathes them. In blackwater fever there may be changes in both the cells and their environment the fact that they show an increased fragility to lyso-lectihin, when compared with normal cells may point to changes in the red cells in the same way as the increased saline fragility in haemolytic jaundice points to red cell abnormality. The fact, however that normal cells are also destroyed when transfused into blackwater fever patients points to some extra-cellular factor as well, and would make it appear that in this disease at least the fundamental defect is not in the red cell but in the environment. Normal cells placed in this abnormal environment are also lysed. In haemolytic jaundice the removal of the spleen stops the periodic haemolysis but does not change the abnormal fragility of the cells (VAUGHAN 1936 HAWKLEY 1934-1936 PARTON 1935 DALAND *et al* 1935 WHITBY

1937) This makes it seem that in haemolytic jaundice there are two factors required for the destruction of the red cells (1) cell abnormality, (2) some factor present in the spleen the removal of which prevents the interaction of the two factors and thus stops the red cell destruction although the cells still retain their abnormal fragility. Whether there are similarly two factors operating in blackwater fever is not possible to say and it is not practicable to discover whether removal of the spleen would prevent blackwater fever.

LLOYD (1941) in his exsanguination experiments on a new born monster, and transfusion of blood from splenectomized and non splenectomized cases of haemolytic jaundice into the monster found that the cells from the splenectomized case became more spherocytic in the monster, and were lysed whilst the cells from the active non-splenectomized case became no more spherocytic than they were in their own circulation. The precise interpretation of these results is not very clear but LLOYD concludes that in haemolytic jaundice there is some inherited defect in the red cells that makes them abnormally susceptible to damage by lyso-lecithin during their passage through even a normal spleen.

The fact that in most of these conditions the spleen is enlarged sometimes grossly has led many investigators to relate the processes taking place in this organ to the events that follow. Certainly its removal in haemolytic jaundice produces results so striking as to warrant such an assumption at least in this disease whether it is similarly responsible in other conditions like blackwater fever or the other haemolytic anaemias is impossible at the moment to say.

Cells leaving the spleen are said to be more spherocytic and fragile than those entering (GRIPWALL, 1938 MELLGREN 1939 HALL and CASTLE, 1940) but none of these experiments proves the point conclusively especially as in most of them narcotics were used which are known to affect red cells (OVERTON 1901).

By labelling cells with fluorescent dyes and transfusing them into haemolyzing subjects and estimating the degree of destruction of labelled and unlabelled cells by means of a cadmium-iron electrode fluorescent microscope, we have been able to follow the fate of such cells and compare the destructibility of both patients and donors cells. We feel that this is the most satisfactory way of dealing with this question rather than observation of cells entering and leaving the spleen in animals under anaesthesia. This work is being reported separately.

Whether there is any fundamental common factor behind all these haemolytic conditions in which the spleen is enlarged is hard to say. Some have incriminated the red cells others a circulating haemolysin, and still others both. Perhaps there is a complex of several factors at work. It is not known whether there is more than one process that can prepare the body for the final haemolytic crisis and whether these processes all work in the same way. In blackwater fever, malaria would appear to be an important preparatory agent, but what exactly it does or how it produces its ultimate effect is quite unknown. The

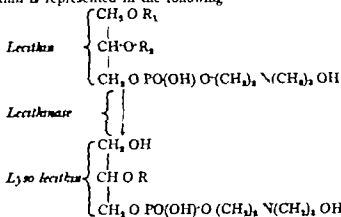
ground having been prepared the trigger may be pulled by any of several agents such as antimalaria treatment (quinine or atabrin) or cold or splenic contraction or the attack may appear without any obvious cause while the patient is lying quietly abed.

In haemolytic jaundice there are also unknown factors which bring about exacerbations of the haemolytic process but here as in blackwater fever the end result is lysis of red cells. The condition of the spleen in so many of these haemolytic states together with the facts that lyso-lecithin has been shown to be produced in this organ that this substance is known to be a powerful *in vitro* haemolytic agent, and that many different authors have attributed to it an important role in the genesis of haemolytic conditions warrants further work on the precise place that lyso-lecithin occupies in all these conditions.

The kinetics of lyso-lecithin haemolysis has so far not been worked out. POWDER distinguishes between simple and complex haemolytic systems, emphasizing that such a distinction is arbitrary. In both these systems his "fundamental equation" would appear to be applicable.

From experiments to be reported later from HELLAWAY's (1933) and HOLDEN's (1935) experiments with snake venom, those of ROY and CHOPRA (1941) and GANGULY (1937) and FELDBERG (1938) work on lecithin and those of MACFARLANE (1941) and others on *Clostridium welchii*, it would appear that lyso-lecithin is to be regarded as falling into the class of complex agents, similar perhaps to the amboceptor-complement-system described by POWDER. Perhaps lyso-lecithin haemolytic systems can best be explained on the basis of colloidal enzyme action (HALDANE, 1930 WALDSCHMIDT LETTZ, 1929). It is suggested that the enzyme lecithinase acting on a substrate of red cells or serum containing lecithin splits the latter into an unsaturated fatty acid and lyso-lecithin, which is powerfully haemolytic.

The reaction between cobra venom lecithinase and lecithin to form lyso-lecithin is represented in the following —

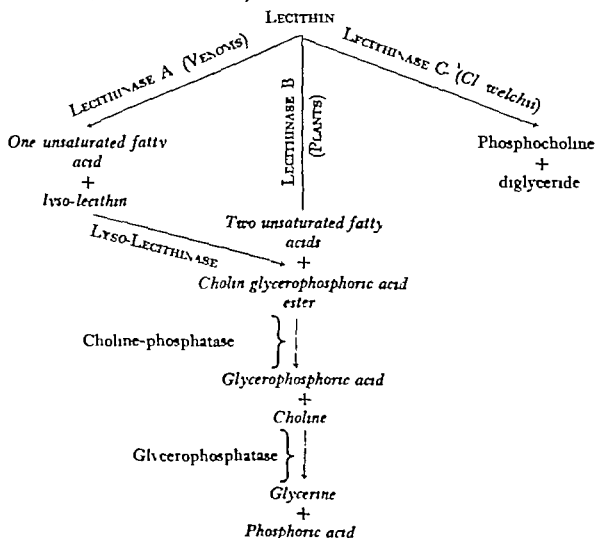


There appear to be three types of lecithinase (BELFANTI 1936 MACFARLANE, 1941) and the final product of their reaction with lecithin is not the

same in all cases. The lecithinase *a* in cobra venom appears to split lecithin into an unsaturated fatty acid and lyso-lecithin that present in plant tissues splits off both fatty acids from lecithin and is known as lecithinase *b*.

Lecithinase *c* which is present in *Cl welchii* toxin filtrates decomposes lecithin with the formation of phosphocholine and a diglyceride—a much more drastic degradation than occurs with either lecithinase *a* or *b*. All these lecithinases have a disintegrative action on the cell membrane or intracellular lipo-protein-complex, whose integrity is dependent upon the presence of lecithin (MACFARLANE 1941). It appears however that neither snake venom nor lyso-lecithin actually disrupts the cell membrane *in vitro* at least initially. They do upset the permeability profoundly and allow haemoglobin to escape, but whether the membrane is subsequently destroyed seems uncertain. It is probable that lecithin from different sources such as that from eggs or soya bean or bran, is not always the same and also that lecithin preparations are mixtures of several lecithins. On hydrolysis these yield varying proportions of saturated and unsaturated fatty acids.

Diagrammatically the reactions of the different lecithinases may be represented as follows. (The scheme takes no account of the possible variations in lecithins from different sources.)



The activity of lecithinase has been shown to be dependent upon the presence of calcium  $++$  being greatly accelerated by this ion and retarded by its absence. We shall take up this aspect of the question when considering the action of lyso-lecithin and snake venoms on various types of red cells.

If as seems probable the mechanics of these lecithinase lecithin lyso-lecithin-haemolytic systems is of the nature of an enzyme action, then it is to be expected that surface areas and volumes would have an important bearing on the results. VALLERY RADOT (1919) and more recently HADEN (1934) and CASTLE (1937) have emphasized this aspect of the problem. We shall consider this question when dealing with the reputed failure of snake venom and lyso-lecithin to haemolyse the red cells of certain animals, such as the sheep and goat.

The lecithinase that occurs in beans may in some way be linked up with the acute haemoglobinuria (favism) that develops in some individuals after eating beans, and which in Greece is indistinguishable from blackwater fever (FOR and KONDI 1933). WARDLE and GREEN (1941) have found that the injection of the fatty acid complexes derived from tape worms (*Monoxia expansionis*) causes an anaemia. It has of course long been known that tape worm infestation gives rise to an anaemia, said to be hyperchromic but the mechanism has so far not been investigated.

It is a curious fact that although the end product of the reaction between snake venom lecithinase and lecithin is lyso-lecithin, the injection of this end substance into baboons as reported above produces no red cell lysis, whereas the injection of snake venom causes haemolysis. Perhaps the explanation of this may be forthcoming on the lines suggested by BRINKMAN and VAN DASI (1920a, 1920b) that the cholesterol lecithin ratio may be a factor of importance in red cell lysis. The injection of lyso-lecithin would not apparently affect this ratio, whereas the injection of snake venom, by liberating lecithinase would allow the latter to split the lecithin in the red cells and/or plasma, and thus upset the ratio. There is no positive evidence one way or the other that this actually takes place.

SULLOW (1932) was unable to confirm these findings of BRINKMAN's regarding cholesterol-lecithin ratios. KLEIN and STONE (1931) have further shown that saponin bacteriolysis of pneumococcus takes place only if cholesterol is added. It would appear however that the inhibiting action of cholesterol is small compared with other *in vivo* inhibitors such as proteins.

The part played by the reticulo-endothelial system in the processes of haemolysis is by no means clear. Quantitative studies are lacking which show precisely what proportion of red cells are actually destroyed by this means. Recent work tending to the view that, even where this system is grossly hypertrophied it is quantitatively and qualitatively unlikely that it can account for the sudden blood cell destruction that occurs in such conditions as we are considering. Very little is known concerning the more likely role that the reticulo-endothelial system may play in the elaboration of possible haemolytins.

In this connection HICKS and OPIE (1942) have recently shown that the macrophages of the spleen elaborate a proteolytic enzyme which, according to them is responsible for the destruction of both red and white cells and that the production of this enzyme runs parallel with blood cell phagocytosis

### SUMMARY

Red cells transfused into a case of haemolysing blackwater fever are destroyed just as readily as the patient's own cells making it appear that it is not the red cells that are at fault in this condition but that there is some circulating haemolysin

By an improved spectrophotometric technique it has now been shown that like those of haemolytic jaundice the red cells from blackwater fever have an increased fragility to lyso-lecithin, although their fragility to saline is normal unlike that of the cells of haemolytic jaundice

These two facts taken together make it seem that in blackwater fever the cells may possess some abnormal feature but that this is probably secondary to more fundamental changes that take place in the cells environment. By using VAN BOROS formula it is possible to demonstrate that spherocytosis occurs in blackwater fever and is accompanied by decreases in diameter-thickness ratio volumes and areas that these changes in blackwater fever are intermediate between those taking place in haemolytic jaundice and normal controls and are not related in blackwater fever to changes in hypotonic saline fragility. It is probable that the initial stage in the destruction of the cells is a change in the permeability of the cell membrane, which allows haemoglobin to escape. The cells have later been seen to swell become 'transparent' and then to disappear. That they have not been broken up can be shown by resuspending them in saline when the 'ghosts' reappear. This phenomenon takes place in both lyso-lecithin and snake venom haemolysis. If the process is allowed to continue the cells are finally disrupted and will not reappear on saline resuspension.

In haemolytic jaundice it seems that there may be some defect in the red cell as well as some splenic factor shown by the fact that splenectomy fails to alter the abnormal fragility of the cells to saline but does stop the periodic haemolysis. A combination of both abnormal cells and splenic factors would seem to be necessary for the destruction of the red cells in this condition. The same cannot be determined for blackwater fever.

The enlargement of the spleen in so many of these haemolytic conditions is regarded by many as of considerable significance. The production of lyso-lecithin as a result of the separation of the cells and plasma in this organ has led to the suggestion that this powerfully haemolytic substance may play a part in the haemolysis of certain of these conditions.

It is possible that lyso-lecithin fragility is in some way related to the action of this substance on the lipoids or lipo-protein complex in the red cell membrane.

It has been shown that the amount of lipid present in the cell envelope is closely related to the dimensions of the cell and that the ability of the cell to increase its volume without being disrupted is related to the lipo-protein ratio in its membrane.

The kinetics of lyso-lecithin haemolysis have not been worked out, but there is some ground for regarding the process as one of enzyme action where the enzyme lecithinase acting on a substrate of red cells or plasma lecithin results in the production of lyso-lecithin or some allied phosphatide. Lecithinase has been shown to be present in many conditions where haemolytic reactions take place such as in fawn snake poisoning *Crotalus* filtrates as well as in the spleen and peripheral blood. The degradation products of the action of lecithinase on lecithin are not always the same nor are the various lecithinases alike.

Although the end product of the action of snake venom lecithinase on lecithin is lyso-lecithin, yet this substance when injected into baboons in relatively huge amounts produces no haemolysis and only a slight shift of the Price-Jones curve to the right. This is in sharp contrast to the haemolysis that follows the injection of snake venom freed of its neurotoxic factor. It is suggested that this difference may be due to the fact that in the former case the lecithin in the cells and or plasma is not disturbed whilst in the case of snake venom injection of the lecithinase present in the venom will split the lecithin of the cells and or plasma and so disturb the intracellular lipo-protein complex.

The part played by the reticulo-endothelial system in the haemolytic process is briefly discussed—the resulting decision being that no precise data are available to enable any conclusions to be reached either upon the part that this system plays in actually destroying red cells or elaborating haemolysins that later lyse the cells.

Proteolytic enzymes may be produced in the macrophages of the reticulo-endothelial system and these have been shown to be capable of destroying red and white cells.

TABLE I  
BLACKWATER FEVER LYSO-LECITHIN FRAGILITY  
(11.11.42.)

Lyso- Lecithin Diluent.	R.B.C. per c.mm.		Per cent. Haemolysis.		Per cent. Haemolysis Spectrophotometric.		Red Cell Appear- ances.	pH of System.
	B.W.F.	Control.	B.W.F.	Control.	B.W.F.	Control.		
Control in 0.85 percent. saline	199 000	197 000	—	—	—	—	Crenated	7.2
1 in 32 L.L.	32 000	39 000	84.0	80	93	83	Spherocytes	7.2
1 " 64 "	43 000	50 000	79.0	75	84	76	"	7.0
1 " 128 "	63 000	112 000	68.0	43	75	48	"	7.1
1 " 256 "	128 000	150 000	36.0	24	40	26	"	7.0
1 " 512 "	151 000	167 000	24.0	15	30	16	"	7.2
1 " 10 <sup>4</sup> "	166 000	193 000	16.0	Nil	20	0	Crenated	7.1
1 " 2 048 "	200 000	19 000	Nil	"	11	0	"	7.1
1 " 4 096 "	195 000	194 000	"	—	Nil	0	"	—

TABLE II:  
BLACKWATER FEVER LYSO-LECITHIN FRAGILITY  
(14.11.42.)

Lyso- Lecithin Diluent.	R.B.C. per c.mm.		Per cent. Haemolysis.		Per cent. Haemolysis Spectrophotometric.		Red Cell Appear- ances.	pH of System.
	B.W.F.	Control.	B.W.F.	Control.	B.W.F.	Control.		
Control in 0.85 percent. saline	134 000	170 000	Nil	Nil	Nil	Nil	Crenated	7.0
1 in 8 L.L.	Nil	Nil	100	100	100	100	"	7.2
1 " 16 "	"	"	100	100	100	100	"	7.2
1 " 32 "	"	"	100	100	100	100	"	7.0
1 " 64 "	"	"	100	100	100	100	"	7.1
1 " 128 "	"	"	100	100	100	90	"	7.0
1 " 256 "	26 000	50 000	80	71	85	78	Spherocytes	7.0
1 " 512 "	39 000	60 000	63	63	73	63	"	7.2
1 " 10 <sup>4</sup> "	103 000	140 000	74	17	25	20	"	7.0
1 " 2 048 "	110 000	153 000	14	8	20	10	"	7.0
1 " 4 096 "	121 000	167 000	8	4.5	10.0	6.0	Crenated	7.1
1 " 8 192 "	131 000	172 000	"	Nil	4.0	1.0	"	7.0
1 " 16,384 "	135 000	170 000	Nil	"	2.0	1.0	"	7.2
1 " 32,768 "	133 000	171 000	"	"	Nil	Nil	"	7.0
1 " 65,536 "	134 000	174 000	"	"	"	"	"	—



TABLE III.

HAEMOLYTIC FRAGILITY OF RED CELLS IN BLACKWATER FEVER, HAEMOLYTIC JAUNDICE, AND CONTROL.

Per cent. saline Diluent.	Per cent. Haemolysis.			pH of System.
	Blackwater Fever	Haemolytic Jaundice	Control	
0.20	100	100	100	6.9
0.1	95	100	100	6.9
0.04	95	100	95	6.9
0.03	85	100	85	6.9
0.02	70	100	90	7.0
0.01	10	100	40	7.0
0.005	5	100	70	6.8
0.004	0	80	5	6.8
0.003	0	63	0	6.8
0.002	0	55	0	6.8
0.001	0	45	0	7.0
0.0005	0	45	0	7.0
0.0004	0	40	0	7.0
0.0003	0	35	0	0
0.0002	0	30	0	6.9
0.0001	0	25	0	6.9
0.00005	0	18	0	6.9
0.00004	0	1	0	6.9
0.00003	0	7	0	6.9
0.00002	0	5	0	6.9
0.00001	0	3	0	6.9
0.000005	0	0	0	6.9

TABLE IV.

HAEMOLYTIC JAUNDICE LYSO-LECTIN FRAGILITY

Lyso- Lection Diluent	R B C. per c.c.m.m		Per cent. Haemolysis.		Per cent. Haemolysis Spectrophotometric		Red Cell Appear- ance.
	Haemo- lytic Jaundice	Control.	Haemo- lytic Jaundice.	Control.	Haemo- lytic Jaundice.	Control.	
Control in 0.85 percent saline							
1 in 16 L.L.	15 000	1 0 000	0 0	0 0	0 0	0 0	Crenated
1     2.	952	95.	99	99	100	100	—
1     4.	3 800	1 900	99	99	100	100	—
1     64	4,250	18 360	97.5	90	100	95	—
1     178	5 40	79 000	97	83	100	85	Spherocytes
1     350	47 800	145 000	78	18	80	70	
1     512	185 000	Nil	14	Nil	20	5	
1     1,024	—	—	—	—	10	3	
1     2,048	—	—	—	—	5	0	Crenated
1     4,096	—	—	—	—	0	0	

TABLE V

Estimation.	Blackwater Fever 11.11.42.	Blackwater Fever 14.11.42.	Haemolytic Jaundice	Normal (Haden).
Crude Mean Cell Volume Haematocrit per cent. — R.B.C. c.mm.	88 $\mu^3$	92 $\mu^3$	85 $\mu^3$	90 $\mu^3$
Mean Cell Diameter (Price Jones)	7.19 $\mu$	7.0 $\mu$	6.85 $\mu$	7.7 $\mu$
Mean Cell Thickness M.C.V. — $\pi \times \left( \frac{\text{M.C.D.}}{2} \right)^2$	2.16 $\mu$	2.39 $\mu$	3.0 $\mu$	1.95 $\mu$
Volume Index (von Boros)	0.8	0.75	0.48	1.0
Corrected Mean Cell Volume = Volume Index $\times$ Normal M.C.V.	72 $\mu^3$	67.5 $\mu^3$	43.2 $\mu^3$	90 $\mu^3$
Diameter-thickness-ratio M.C.D. — M.C.T	3.3:1	2.9:1	1.95:1	4.0:1
Volume Thickness Index Crude M.C.V. — Corrected M.C.V.	1.23	1.36	1.98	1.0
Surface Area = 0.64 $\times \pi D^2$	104 $\mu^2$	95 $\mu^2$	68 $\mu^2$	117 $\mu^2$

## REFERENCES

- BELFANTI S. CONTARDI A. & ERCOLI A. (1936) *Ergebn. Enzymforsch.* 5, 213  
 BERGENHEIM B. & FAHRAEUS, R. (1936) *Z. ges. exp. Med.* 97, 555  
 BODANSKY M. (1931) *Proc. Soc. exp. Biol. Med.* 28, 632.  
 ——— (1932) *J. cell comp. Physiol.* 1, 429  
 ——— (1933) *J. exp. Biol.* 10, 59  
 BRINKMAN R. & VAN DAM E. (1920a). *Biochem. Z.* 108, 35  
 ——— & ——— (1920b) *Ibid.* 108, 52  
 CASTLE, W. B. (1937) *Arch. intern. Med.* 60, 949  
 Dacie, J. V. (1941) *J. Path. Bact.* 52, 331  
 DALAND G. A. & WORTLEY K. (1935) *J. Lab. clin. Med.* 20, 1122.  
 DZIEDMAN A. J. (1939) *J. cell comp. Physiol.* 14, 103

many of these showed evidence suggestive of iron deficiency and also of a deficiency which responded to liver. A dual deficiency was often present.

#### TECHNICAL DIFFICULTIES.

1 *The Normal Blood Count of Healthy Africans is not known.* This is a hyperendemic area of malaria, and the hookworm infestation is high and syphilis is rife—to mention but three diseases. Surveys of prisoners conducted by HENNESSY (1937) and VINT (1939) reveal low standards when compared with those of Europeans. Uganda is 2,000–5,000 feet above sea level and some increase in the normal haemoglobin and red cell count might be expected.

A small investigation of African medical students, apparently in good health, has revealed no difference between their red cell and haemoglobin standards and those of the European. The number of these observations at the present time is very limited—they will be extended and in time may furnish a basis of comparison. Our experience agrees with workers in India who find no significant difference between well-fed Indians and Europeans.

2 *Haemoglobin Estimations.*—Since gas is not available in many tropical hospitals the Haldane method and scale (100 per cent. = 13.8 grammes of Hb.) is seldom used. Most use the Sahli scale (100 per cent. = 17.2 grammes of Hb.), and employ the acid haematin method although this probably is not very accurate. The Sahli scale gives much lower figures than the Haldane scale, and a much lower colour index (C.I.). In Britain a C.I. over unity in a severe anaemia suggests pernicious anaemia, but with the Sahli scale any C.I. over 0.85 should suggest hyperchromia and pernicious anaemia. If this is not recognized many hyperchromic cases may be missed. To overcome this difficulty we now employ a corrected Sahli scale where 100 per cent. = 14.5 grammes of Hb. and the normal C.I. is about unity. In addition it is almost impossible to convert accurately the haemoglobin scale into grammes of haemoglobin for the methods suggested until recently were elaborate and beyond our command. We have been forced to accept the specifications of the makers. This introduces an important source of error into the determination of the Hb. in grammes and therefore of the mean corpuscular haemoglobin concentration (M.C.H.C.). As low values for the latter are one of the surest indications we possess of iron deficiency and are extensively used as such in this article, an element of error is present here. It is considered that the present scale used in this hospital is fairly accurate largely because no case had a figure of M.C.H.C. which exceeded the upper limit of the normal range of European M.C.H.C. (PRICE, JONES, VAUGHAN and GODDARD, 1935), and yet some cases approximated to this level. Although open to suspicion, no amount of technical error will explain the large variations found in the figures obtained for M.C.H.C. (Fig. 1) and it is considered that many of the anaemias were hypochromic.

3 *The Mean Corpuscular Volume Estimations.*—A high-speed electrical

centrifuge was employed. Its rate of spinning was unknown, but it packed red cells completely in 30 minutes. Fresh oxalated blood, employing Wintrobe's double salt, was spun for 45 minutes to ensure complete packing. It is felt that full packing was obtained and that these figures are reliable. In my opinion

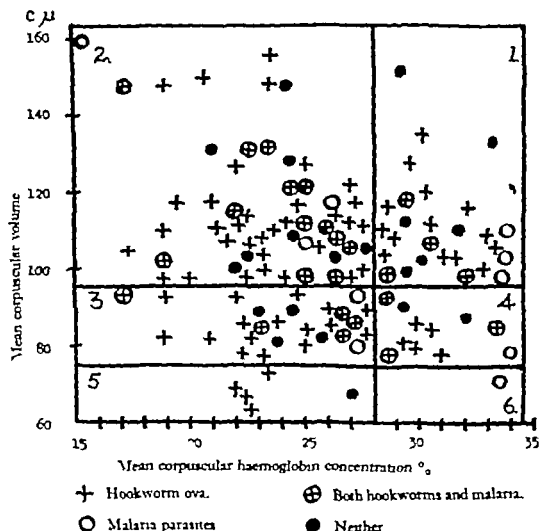


FIG. 1.—SCATTER DISTRIBUTION OF 134 CASES OF ANAEMIA WITH REGARD TO CELL VOLUME (M.C.V.) AND HAEMOGLOBIN CONCENTRATION (M.C.H.C.)

- |                            |                            |
|----------------------------|----------------------------|
| 1 Macrocytic orthochromic. | 2 Macrocytic hypochromic.  |
| 3 Normocytic hypochromic.  | 4 Normocytic orthochromic. |
| 5 Microcytic hypochromic.  | 6 Microcytic orthochromic. |

a fairly large element of error is introduced when the packed cell volume is very small, and thus in the final figure for mean corpuscular volume but apart from this I consider the figure is reliable. Employed on a few anæmic Europeans this method has produced figures which have correlated with the other haematological findings and eight normal Africans fell within the normal European

range (PRICE JONES *et al* loc cit.). It is therefore considered that high figures of mean corpuscular volume were reliable and that many of the anaemias were macrocytic (Fig 1).

4 *The Price-Jones Curve*—It appears to be extremely difficult to spread evenly the red cells obtained from our severely anaemic cases—a point discussed in the paper on morphology. The larger orthochromic cells tend to collect at the edges and towards the tail; the smaller hypochromic cells tend to collect in the central portions of the smear of peripheral blood. Fair sampling which is essential for the Price-Jones technique, becomes an arbitrary procedure. Others have experienced the same difficulty (see discussion after HAMILTON FAIRLEY *et al* 1938). It is therefore difficult to estimate accurately the mean diameter (M.D.), and therefore the mean corpuscular average thickness (M.C.A.T.).

5 *Helminthic Ova*.—Our method probably misses very light infections and is described elsewhere (TROWELL, 1939). It is a floatation method. Negative reports are repeated two or three times.

#### *Classification of anaemia by the deficiencies present*

It appears inevitable that an attempt will be made to classify the anaemias seen in the tropics, in terms of the deficiency or deficiencies present, whether these deficiencies are due to disease or to diet. If no deficiency is found to be present, then a blood destroying disease like malaria may well be the sole cause of the anaemia and therapy will be directed towards the specific treatment of this disease. This should produce a complete cure and this is what is seen to occur in the malarial anaemia of well fed Europeans or Asians. In them it is not necessary to give iron or liver to restore the blood count to normal or to maintain it at a normal level provided that no relapses of the malaria occur.

It will not prove easy to define the nature of the deficiencies present in any case of anaemia seen in the natives of the tropics, and this approach to the question of anaemia will be fraught with many difficulties. It will be easy to define iron deficiency for this subject has been very adequately investigated in temperate climates and no differences have been detected in the blood picture in the tropics even when hookworms occasion the iron deficiency (apart from the detail of eosinophilia). It, however, is when an anaemia is found to react also to liver and perhaps to marmite that it will be difficult to assess the significance of this finding. That this would suggest a pernicious anaemia type of deficiency will be generally conceded especially if the anaemia proved refractory to iron therapy and additional confirmation will be lent if the anaemia is macrocytic and the bone marrow shows any megaloblastic change. Once it is granted that a pernicious anaemia type of deficiency is present, it will be necessary to ascertain, if possible how this deficiency arose. Owing to the very great rarity of pernicious anaemia in all natives of the tropics, it will be natural to link this deficiency macrocytic anaemia with nutritional (tropical) macrocytic

anaemia. It will then be found that our knowledge of this anaemia is limited, and in many respects confusing.

In addition those who attempt to classify their anaemias by the deficiencies present may find as have others including myself, that the majority of cases appear to have two deficiencies present, that of iron deficiency and one of the pernicious anaemia group. This may well produce a confusion of hypochromia and hyperchromia, of microcytosis and macrocytosis, and many will consider this confusion intolerable and will abandon the classification of anaemia in terms of deficiency and will return to the conception of secondary anaemia that is anaemia secondary to hookworm infestations, bilharziasis, and other tropical diseases. Nevertheless the deficiencies present supply the key to the treatment and to the blood picture.

#### NUTRITIONAL MACROCYTIC ANAEMIA.

In recent years reports have been published largely in India but also in many other tropical countries, in which a macrocytic anaemia has been described which is curable by administering liver in an appropriate dose and form. All reports draw a sharp distinction between this group of cases and pernicious anaemia which is admitted to be a very rare disease in natives of the tropics, and indeed I have never seen a typical case in an African native. The chief point of distinction, in my opinion between these two anaemias is that pernicious anaemia is a permanent disease, whereas on the other hand all anaemias put in the nutritional macrocytic group are not permanent. In addition sub-acute combined degeneration has never been described in nutritional macrocytic anaemia. No other point can, in the present stage of our knowledge be regarded as unequivocal. Many would state that marmite, which is stated to be rich in extrinsic factor cures only nutritional macrocytic anaemia and not pernicious anaemia but others do not agree with this statement. From 1 to 2 ozs a day are required and the dose employed is sometimes inadequate and may thus explain some of the failures.

It does however, follow that the test meal results are of cardinal importance in distinguishing these two anaemias. It is true that achlorhydria has occasionally been reported in an anaemia of the nutritional macrocytic group, and a fair number have reported hypochlorhydria, especially during pregnancy but most observers find a fair secretion of hydrochloric acid.

It is true that a few authors (MUDALIAR and MENON 1942) consider that the secretion of intrinsic factor is at fault in this anaemia (or at least in the tropical variety seen in pregnant Indian women) but most workers have considered that the diet was probably defective in extrinsic factor and that cases could be cured by large doses of marmite. The aetiology of this anaemia may well remain obscure for some considerable time, largely because it is extremely difficult to assess quantitatively the amount of intrinsic factor in the gastric juice or to determine if any diet is deficient in extrinsic factor. To test for

intrinsic factor it is necessary to have cases of Addisonian pernicious anaemia in relapse and to give them beef incubated with the gastric juice which is being assayed but cases of pernicious anaemia, which are necessary for this test, are unfortunately very rare in the tropics. On the other hand very little is known about the distribution of extrinsic factor. It is known to be present in meat and possibly in certain green vegetables, but apart from this almost nothing is known about its distribution in various foodstuffs and its assay presents great technical problems. Certainly all statements, of which many abound, that the diet in these cases was adequate in extrinsic factor must be received with great caution.

In this group of nutritional macrocytic anaemias (which are as far as we know unassociated with gastro-intestinal or liver disease), it is impossible to say at present if only one anaemia or whether a group of anaemias is present. Thus there is an attempt to divide this group into the megaloblastic anaemia of pregnancy (pernicious anaemia of pregnancy) seen in temperate climates and the tropical macrocytic anaemia seen in pregnant women in the tropics but since the latter disease has been described in Greece any distinction in terms of geography now appears doubtful. Many would make a sharp distinction between the deficiency macrocytic anaemia of pregnancy and the deficiency macrocytic anaemia seen in non pregnant women, in men and in children. No distinction apart from pregnancy is however known and since all deficiencies tend to become more marked during pregnancy the onus of proof should lie with those who desire to make this distinction. The foetus in most of these cases is born with a normal blood count and may well create a serious deficiency in the mother. Other attempts have been made to create fresh varieties according to the reaction of these cases to marmite or to certain liver extracts. Much disagreement has occurred concerning the dosage and form of all liver extracts used in this anaemia so that, until the position is clarified, no distinction can be admitted by reason of this. The position of the present writer is that there exist no sure grounds for distinguishing at the present time any special varieties of nutritional macrocytic anaemia which must be regarded as a single clinical entity although further knowledge may demonstrate that there are real differences and that they constitute a group of allied anaemias. In a recent article in the *Lancet* the present writer has tried to review our present knowledge of this anaemia, and has given a bibliography (Frowell, 1943).

Indeed, if CASTLE's theory is correct, namely that extrinsic factor is acted upon by intrinsic factor and converted into a pernicious anaemia factor then a deficiency anaemia, due to an inadequate intake of extrinsic factor is not only possible but probable. If it does not occur then it must cast doubt upon the whole of CASTLE's hypothesis. If it does occur then it may occur at all ages in all races sexes and climates. Although little is known concerning the distribution of extrinsic factor in various African articles of diet, yet it is extremely unlikely that it is evenly distributed in every kind of food. It is possible that

increased amounts of extrinsic factor and of iron are needed in many diseases which destroy blood and this may explain why these deficiencies commonly occur with malaria and ankylostomiasis in natives of Uganda

Only two other points will be made. First some observations suggest that the mean diameter (M.D.) is often only slightly macrocytic in this anaemia or may even fall within the normal range. The number of investigations is small but it is clearly reported by several observers in all varieties of this anaemia. All investigators stress the fact that the mean corpuscular volume (M.C.V.) is always raised. It follows that to detect the macrocytosis of this anaemia it is necessary to estimate M.C.V. and that the examination of stained smears and the measurement of the mean diameter (M.D.) may fail to detect this anaemia. Secondly although some cases respond to marmite and a fair number to half a pound of lightly cooked liver eaten daily the most reliable of treatments is the parenteral administration of crude liver extracts. Liver extract for injection (B.D.H.) \* 12 to 20 c.c. weekly or campolon in the same amount. Pregnancy demands a still larger dosage. Refined liver extracts like anahaemin are usually effective if given in an enormous dosage of 12 to 15 c.c. weekly an amount derived from a much larger weight of liver than the corresponding volume of a crude extract. Some have reported that some refined extracts, designed for use in pernicious anaemia, are completely or relatively inactive in this anaemia.

Many describe a non haemolytic and a haemolytic variety, the latter being characterized by fever, reticulocytosis, jaundice and a splenomegaly which often extends beyond the umbilicus. It will be seen how easy it is to confuse the haemolytic variety with chronic malarial splenomegaly and anaemia, or with kala azar or bilharzial splenomegalies and anaemia. Fortunately both of the latter diseases are almost unknown in this part of Uganda.

### DIET

Patients divided themselves into two groups the indigenous Ganda, Nyoro and Nkole tribes and the immigrant Ruanda tribes members of which had walked from 300 to 600 miles from the Belgian Congo. The former are peasant agriculturists who subsist on the staple food of cooked plantains and sweet potatoes with certain additions of beans and groundnuts, and the poorer members of these tribes take cassava. Leafy vegetables are not commonly taken and fruit is almost unknown. Meat would be taken only about once or twice a month. This is due to poverty and the scarcity of cattle, sheep, goats and poultry. Fish is only taken by a few who live near the shores of Lake Victoria. Milk is almost unknown. The diet tends to be very monotonous, being limited to only a few articles. It is poor in protein of good biological

\* Much of the work reported in his article arose out of an attempt to find what liver fractions are most effective in nutritional macrocytic anaemia. Liver extract for injection (B.D.H.) was used in certain cases others received experimental fractions. Thanks are due to the British Drug Houses for liver injections sent for trial.



value deficient in fat and probably deficient in iron. Deficiencies in salts, vitamins and extrinsic factor cannot be assessed. Cases of anaemia are common in the indigenous tribes (59.6 per cent.). Upper classes in native society are better fed and seldom contract severe anaemia.

The immigrant Ruanda tribes come to work in Uganda and they suffer great hardships on the road being exposed to relapsing fever and to malaria to which they have little immunity and they may be very short of food, and subsist mainly on sweet potatoes, cassava and plantains. Having arrived in Uganda, they must obtain work or they may be in want. They earn about fourpence a day and are often not given food. They contract severe attacks of malaria and suffer from hookworm disease, taeniasis, ascariasis and amoebiasis. They exist in conditions of great poverty. Deficiency diseases, mainly those of vitamin A and of the B complex are common. They provide many cases of anaemia (40.4 per cent.).

The hospital makes provision largely for immigrant male labour and male admissions are about four times as numerous as female so little can be said as to whether anaemia is commoner in either sex.

The hospital diet taken by almost all of these patients consisted mainly of cooked plantains supplemented by a certain amount of sweet potato and some beans. Meat would vary from 1 to 4 ozs a week. This diet itself is possibly deficient in both iron and extrinsic factor but is regarded as good fare by the immigrant labour.

### PERSONAL OBSERVATIONS

#### THE FIRST PHASE (1896-1938) CLASSIFICATION ALONG TRADITIONAL LINES

248 cases      80 deaths

Malarial anaemia	51 cases, 9 deaths
Hookworm anaemia	119 cases, 18 deaths
Malarial and ankyllostomiasis	64 cases, 10 deaths
Nutritional macrocytic anaemia	58 cases, 13 deaths
Miscellaneous group	26 cases, 11 deaths

The heavy mortality rate of 20 per cent. is a comment on the inadequacy and incorrectness of treatment. The third and fifth groups are not analyzed any further as they are too complex and cast little light on the aetiology of anaemia in Uganda.

#### Malarial Anaemia

*P. vivax* 1 case    *P. malariae* 8 cases (1 fatal)

*P. falciparum* 32 cases (5 fatal). Double infections (*malariae* and *falciparum*), 10 cases (2 fatal)

The mean blood count for the group was as follows:—

R.B.C. 2,400,000

Hb 39 per cent. 4.6 grammes

C.I. 0.81

The following difficulties were encountered —

1 The group was certainly not a homogeneous group C.I. varied from 0.4 to 1.3

2 Twenty-seven cases having C.I. over 1.0 were then arbitrarily transferred to nutritional macrocytic anaemia

3 Only half the cases showed an adequate response to quinine (2 grammes daily) and ferrous sulphate (2 to 4 grammes daily).

### Hookworm Anaemia

Only *Necator americanus* has been found

The mean blood count for the group was as follows —

R.B.C. 2,340 000      Hb 35 per cent., 3.9 grammes      C.I. 0.76

The following difficulties were encountered —

1 The group was certainly not a homogeneous group, C.I. varied from 0.4 to 1.3

2 At the end of a month's treatment with deworming (repeated doses of carbon tetrachloride 3 to 4 c.c. and oil of chenopodium, 1 c.c. in a saline purgative on an empty stomach) and ferrous sulphate (2 to 4 grammes daily), only half of the cases were still improving but the blood count was only about two thirds regenerated

3 Thirteen cases having a C.I. over unity were arbitrarily transferred to the nutritional macrocytic anaemia group but the latter deficiency masked by hypochromia might have extended into other members of this group

4 2 c.c. of campolon were accidentally given to a case whose C.I. was 0.60 yet it induced a reticulocytosis of 17 per cent. and a rise of the blood count

5 The Price-Jones curve was plotted only in five cases and gave the following unexpected results —

Case	C.I.	M.D. ( $\mu$ )	$\sigma$	V	Macrocytes per cent	Microcytes per cent
1	0.84	7.820	1.209	15.047	26.6	1.0
2	0.84	7.088	0.718	10.125	—	—
3	0.72	7.428	0.739	9.975	4.8	—
4	0.72	6.953	0.965	13.875	2.4	6.8
5	0.60	6.450	0.748	11.540	—	11.8

### Nutritional Macrocytic Anaemia.

Two pregnant women, three non pregnant women, fifty three males

The mean blood count for the group was as follows —

R.B.C. 2,040 000      Hb 46 per cent 6.5 grammes      C.I. 1.15

The following difficulties were encountered —

1 Twenty seven cases previously classified as malarial anaemia, but having a C.I. over unity, were transferred to this group, but it could not be

certain that nutritional macrocytic anaemia did not extend further into the malarial group

2. Thirteen cases previously classified as hookworm anaemia, were similarly transferred, but it seemed even more probable that nutritional macrocytic anaemia, masked by hypochromia, extended further into the group of hookworm anaemias

3. Eight cases, previously classified as splenic anaemia or the Banti syndrome, were similarly transferred estimations of M.D. and the Price Jones curve having proved a macrocytosis (TROWELL, 1940).

4. Ten of this group were accidentally given iron and all improved considerably

5. When given campolon, 10 c.c. a reticulocytosis of 35 per cent. followed, but on an average the C.I. dropped from 1.08 to 0.60 as iron-deficiency became apparent.

All these considerations suggest that a dual deficiency might have operated in some of these cases

#### THE SECOND PHASE (1939-1941). REVISED CLASSIFICATION BY DEFICIENCIES.

The usual classification was abandoned in favour of the following —

1. Ascertain if deficiencies occur and attempt to define them.
2. Ascertain what diseases are accentuating or causing these deficiencies or in any way destroying blood (*e.g.* ankylostomiasis, malaria)
3. Ascertain what other infections or serious pathological conditions (*e.g.* tuberculosis, nephritis), are present which may inhibit erythropoiesis

Some 134 cases were classified as follows (Fig. 1 p. 21) —

27 macrocytic orthochromic anaemia	11 normocytic orthochromic anaemia.
63 macrocytic hypochromic anaemia	5 macrocytic hypochromic anaemia.
27 normocytic hypochromic anaemia.	1 macrocytic orthochromic anaemia.

It must be clearly understood what these terms mean. The normal range of mean corpuscular volume given by PRICE JONES, VABOYAN and GODDARD (1935) was calculated on the basis of the normal range being plus or minus three times the standard deviation, and was found to vary from 75.144 c.μ. to 96.096 c.μ. These figures define macrocytic, normocytic and macrocytic, and these terms (as used subsequently in this article) have no reference to the mean diameter (M.D.) or the Price-Jones curve. Similarly these investigators found a normal range of mean corpuscular haemoglobin concentration (M.C.H.C.) to be from 28.17 to 34.35 per cent. and these figures define hypochromia and orthochromia (as used subsequently in this article) and these terms have no reference to the colour index, in which hyperchromia can occur.

The question then emerged what was the significance of these groups. It was assumed that macrocytic orthochromic anaemia was uncomplicated nutritional macrocytic anaemia and that little or no iron deficiency was present, but the latter point has not been investigated. Test meals excluded the presence

of pernicious anaemia. It was also considered that microcytic hypochromic anaemia and microcytic orthochromic anaemia were probably due to pure iron-deficiency, but this again has been inadequately investigated.

The facts which came, however, to dominate the situation were the two large intermediate groups of sixty three cases of macrocytic hypochromic anaemia and of twenty-seven cases of normocytic hypochromic anaemia. What was the aetiology of the anaemias found in these two groups? In the first place all cases having serious intercurrent disease (nephritis, tuberculosis, hepatitis etc.) or sickle-cell anaemia (three cases) were excluded, since treatment was unlikely to succeed and it was unlikely that they were cases of deficiency anaemia. In this way some sixteen cases were excluded leaving some fifty cases of macrocytic hypochromic anaemia and some twenty four cases of normocytic anaemia in which anaemia appeared to be the primary condition. An analysis is now given of these seventy four cases in these two groups.

## GROUP II MACROCYTIC HYPOCHROMIC ANAEMIA (FIFTY CASES)

Seven deaths. Pneumonia 1, empyema 1, severe anaemia Hb 10 per cent.  
2 pellagra 1, inanition 1, haemorrhage after splenectomy 1.

Sex—Thirty six males, fourteen females (none pregnant). All Africans.

Tribes—Twenty three indigenous, twenty seven immigrants.

Ages—1 to 60 years, mean about 27 years.

Mean Blood Count (and Range)—R.B.C. 2.01 millions (0.86 to 4.10), Hb 34.1 per cent (10 to 75), 3.85 grammes, C.I. 0.85 (0.54 to 1.11), M.C.V. 115.8 c.μ. (97 to 164), M.C.H.C. 22.8 per cent. (12.7 to 27.8).

Fever (twenty three cases)—99° to 101° F (excluding malaria and infections) for 1 to 3 weeks.

Reticulocytosis over 2 per cent (forty four cases), mean 5.6 per cent. (range 2.3 to 15).

Bilirubin in Serum above 1.5 mg per cent. Eight increased out of twenty six tested, mean of those increased 2.51 mg (range 1.8 to 4.7), all except two were indirect positives. All having increased serum bilirubin had Grade III and IV spleens except one Grade I.

Splenomegaly—Grade I six cases, Grade II four cases, Grade III, ten cases, Grade IV eight cases. Total twenty-eight out of fifty cases (Hackett-Schöffner classification.)

Test Meal—Achlorhydria, histamine fast, one case (tested three times), hypochlorhydria one case, normal acidity seven cases, hyperchlorhydria seven cases, range of maxima 60 to 90  $\frac{N}{10}$  HCl (all compared with Bennett and Ryle's British standards). Total sixteen cases.

Malaria.—Eleven sub-tertian, two quartan.

Ankylostomiasis.—Forty five cases of fifty often heavy infections.

Taeniasis five, ascariasis four amoebiasis five congestive heart failure (severe) four beriberi oedema two pellagra two undulant fever one relapsing fever one pneumonia two

*Kahn Test*—Positive thirty five out of fifty (yaws and syphilis) The incidence of positives in routine male admissions to this hospital is about 67 per cent

The only case with a histamine fast achlorhydria occurred in a young lad of 16 years showing atypical signs of pellagra which responded well to nicotinic acid. In view of his age and the associated pellagra, it is considered doubtful if this was a case of pernicious anaemia.

Of seven cases tried on iron alone (2 to 4 grammes ferrous sulphate daily) all responded but four of them became stationary after the following number of weeks, 2, 4 2, 1 two cases still seemed to be slowly improving at the end of 6 and 8 weeks respectively and had climbed to R.B.C. 4.4 millions, Hb 84 per cent and R.B.C. 4.3 millions Hb 72 per cent., and were then lost to observation. They were both cases having slight macrocytosis, M.C.V. being 100 and 106 c $\mu$  but hypochromia was severe, M.C.H.C. being 19 and 23.7 per cent. It is considered that if their diet were rich enough in extrinsic factor and the ankylostomiasis, malaria and other diseases were treated that they would probably eventually struggle back to a normal blood count, hastened perhaps by the addition at any time of a little liver. The latter point was not proved and the dual deficiency is uncertain.

Two cases were given liver only one case (M.C.V. 146 c $\mu$ , M.C.H.C. 24.5 per cent) had nutritional macrocytic anaemia as the main deficiency he recovered from R.B.C. 1.5 millions Hb 39 per cent to R.B.C. 3.65 millions Hb 78 per cent in 2 weeks on injections of neo-hepatex 4 c.c. daily and he had reticulocyte response to 13.9 per cent. and then recovered well on marmite three teaspoons daily to R.B.C. 4.5 millions, Hb 90 per cent the spleen also shrunk from below the umbilicus to the left costal margin. It is considered in this case that iron deficiency was a minor matter and that he was a doubtful case of the dual deficiency. The other case was given liver only (R.B.C. 1.4 millions Hb 30 per cent, M.C.V. 151 c $\mu$ , M.C.H.C. 19.5 per cent.) he was seriously deficient in both the liver principle and iron given liver he made an incomplete response and after 10 weeks had only reached R.B.C. 3.4 millions Hb 72 per cent. It is considered that recovery might have been more speedy and more effective if iron had been given, but he was then lost to observation and the point was never proved.

Thirty five cases were given both iron and liver sometimes separately and the double reticulocyte response watched sometimes they were given together when the blood count always rose in a most satisfactory manner if intercurrent serious disease was absent and malaria, if active, was treated. Two cases tried on marmite (60 grammes daily) responded fairly well, but the response to marmite was inadequately studied.

### GROUP III NORMOCYTIC HYPOCHROMIC ANAEMIA. TWENTY-FOUR CASES

Possibly a dual deficiency anaemia, possibly pure iron deficiency anaemia.

Two deaths Severe anaemia, possibly aplastic one, infantile pellagra,"

one

*Sex*—Fourteen males ten females (none pregnant)

*Tribes*—Eighteen indigenous, six immigrant

*Ages*— $1\frac{1}{2}$  to 55 years, mean about 28 years

*Mean Blood Count (and Range)*—R.B.C. 2.58 millions (1.05 to 4.67) Hb 39 per cent (12 to 78) M.C.V. 87.7 c  $\mu$ . (76 to 95.9) M.C.H.C. 23.91 per cent. (17.2 to 27.8)

*Fever*—Low fever 99° to 100° F. nine cases

*Reticulocytes over 2 per cent*—Eighteen cases

*Bilirubin in Serum above 1.5 mg per cent*—Three out of twelve tested, mean 1.6 (range 1.5 to 1.7)

*Splenomegaly*—Grade I four cases Grade II three cases, Grade III four cases Total eleven cases out of twenty four

*Test Meal*—Five cases two hypochlorhydria two normal acidity, one hyperchlorhydria

*Malaria*.—Four sub-tertian, two quartan.

*Ankylostomiasis*—Twenty cases out of twenty four mostly heavy infections

*Taeniasis* one *ascariasis* none *amoebiasis* three *pellagra* one severe congestive heart failure three *pneumonia* one *pleural effusion*, one enlarged liver three cases (three four and five fingers enlargement of liver below costal margin)—no obvious cause except associated with splenomegaly Grade II or III

This group was not investigated as thoroughly as the macrocytic group largely because experimental work was being done on certain liver fractions for injection and it was assumed at first that there was no deficiency of the liver principle in this group of normocytic hypochromic anaemia. It was assumed that hookworms and iron deficiency accounted for most of the cases. Cases complicated by malaria were given quinine and iron and are not included in the following analysis. The other cases were therefore dewormed several times (or rather had the load much reduced) and were given ferrous sulphate 2 to 4 grammes daily. In this way some seventeen cases were treated eight appeared to do well but were only kept under observation for about 2 weeks on an average one case failed to respond three remained stationary of whom one died five improved at first but became stationary at a mean Hb of 52 per cent (range 45 to 60) having commenced treatment with a mean Hb of 24 per cent (range 10 to 30) and remained under observation for an average period of just over 4 weeks. Only two cases had the blood picture analyzed during the stationary period both had changed into macrocytic hypochromic anaemia—

I M.C.V. 95.2 c  $\mu$ . M.C.H.C. 17 per cent  $\rightarrow$  M.C.V. 108.4 c  $\mu$ . M.C.H.C. 27.7 per cent

2. M.C.V. 82.2 c $\mu$  M.C.H.C. 22.5 per cent.  $\rightarrow$  M.C.V. 129 c $\mu$   
M.C.H.C. 26.4 per cent.

Four cases were given liver and iron —

1. Ankylostomiasis and lobar pneumonia, deworming and sulphapyridine  
Hb 56  $\rightarrow$  88 per cent in 11 days.
2. Ankylostomiasis and a light relapsing quartan malaria, aged 1½ years.  
Hb 13  $\rightarrow$  22 per cent.  
R.B.C. 0.7  $\rightarrow$  0.84 millions } in 5 weeks on iron and much quinine.

M.C.V. 87.2 c $\mu$ . M.C.H.C. 27.9 per cent.

Then given neo hepatex 2 c.c. daily (= adult dose 30 c.c. daily)

Reticulocyte response to 9 per cent. and

- Hb 22  $\rightarrow$  65 per cent.  
R.B.C. 0.85  $\rightarrow$  3.50 millions } in 3 weeks on liver injections and iron.

3. Infantile pellagra, sub-tertian malaria, ankylostomiasis, aged 3 years.

Death within 12 days, slight improvement of anaemia Too complicated a case to analyze the response to treatment

4. Ankylostomiasis sub-tertian malaria, taeniasis, ascariasis.

Female aged 30

On iron and quinine for 2 weeks —

R.B.C. 0.79  $\rightarrow$  0.74 million Hb 19  $\rightarrow$  18 per cent M.C.V. 80 c $\mu$ . M.C.H.C. 27.3 per cent., reticulocytes constantly 17 to 20 per cent. spleen Grade I low fever bilirubin 2 mg (indirect positive) test meal normal acidity marrow some megaloblastic change Given liver injection (B.D.H.) 14 c.c., reticulocytes fell from 20 to 4 per cent. and recovery of R.B.C. to 4.5 millions and Hb to 80 per cent.

Two other cases given liver and iron showed a fair response, one only remained under observation 1 week, the other became stationary at Hb 72 per cent. having risen from 23 per cent., but had a pleural effusion, probably tuberculous, to inhibit erythropoiesis.

It is therefore considered that a certain number of cases in this normocytic hypochromic group were cases of a dual deficiency. Iron deficiency was usually the major deficiency and in time a certain number might have struggled to a normal blood count if given iron alone, but a certain number did not. Given a diet rich in extrinsic factor this improvement should be accelerated given liver this recovery became in certain cases more speedy. Certain cases appeared to have so marked a deficiency of the liver principle that they did not respond until given liver.

Suggestive confirmation of the dual deficiency was obtained by the cases showing traces of megaloblastic development in the bone marrow the cases showing signs suggestive of haemolysis (reticulocytosis, fever splenomegaly and jaundice) and the transition into almost pure nutritional macrocytic (orthochromic) anaemia (M.C.H.C. being almost normal), namely 27.7 and 26.4 per cent. respectively if given iron alone. In addition there was the

response of four cases to liver. In this group of normocytic hypochromic anaemia the macrocytosis of one deficiency appears to be masked by the microcytosis of the other.

### THE EFFECT OF CORRECTING ONLY ONE DEFICIENCY

If only one deficiency was corrected in the two intermediate groups of anaemia the result appeared to depend on whether the deficiency which was being treated played a major part in the dual deficiency. Thus if iron was given to cases in which iron deficiency was the major one while the liver principle deficiency was the minor one (that is the cell was usually normocytic or slightly macrocytic) the anaemia improved but the corpuscular volume (M.C.V.) rose and the haemoglobin saturation (M.C.H.C.) rose (Fig. 2). Cases did not move (diagrammatically) towards the square which represented normal blood but towards the rectangle which represented nutritional macrocytic anaemia and two cases, previously normocytic and hypochromic changed into that of an almost pure liver principle deficiency.

On the other hand if liver was given (Fig. 3) to cases in which it was the major deficiency (shown usually by severe macrocytosis mean corpuscular volume exceeding  $110 \text{ c}\mu$ ) then the anaemia became less macrocytic and moved towards the position held by normal blood (two cases). On the other hand if liver and iron were both given the anaemia tended to change into the square representing normal blood (one case) or if iron deficiency was slight it might change temporarily into nutritional macrocytic anaemia. The complete recovery of cases of uncomplicated nutritional macrocytic anaemia on liver alone is shown in the same diagram.

Much has yet to be learnt about this complex problem and it would appear to be unwise to generalize on the few cases that have been investigated. In due course it is hoped that more cases will have been adequately investigated and detailed case reports will be published. The present shortage of liver extracts will however delay investigation.

### IRON DEFICIENCY AND NUTRITIONAL MACROCYTIC ANAEMIA.

The first clear reference to an anaemia due to this dual deficiency was made by NAPIER and MAJUMDAR (1938b). They found great difficulty in classifying the anaemias seen by them in pregnant Indian women and recorded some fifty two cases. Classification either by the colour index or by the mean corpuscular haemoglobin (M.C.H.) did not divide up cases into those showing an iron-deficiency anaemia and those with nutritional macrocytic anaemia, so that they concluded that most cases showed both deficiencies. It is regrettable that they were unable to accept the accuracy of the figures for packed cell volume and so were unable to estimate M.C.V. or M.C.H.C. NAPIER *et al* (1938a) reported two cases of this dual deficiency anaemia amidst other typical cases of nutritional macrocytic anaemia (their Group b Cases 4 and 6) both



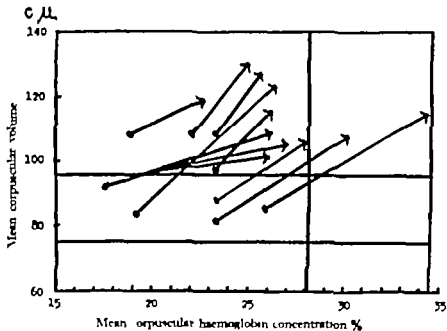


FIG. 2.—EFFECT OF CORRECTING IRON DEFICIENCY ALONE IN DIMORPHIC ANAEMIA.

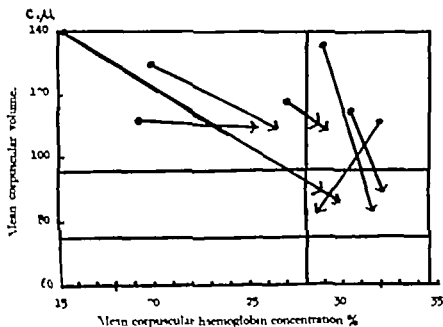


FIG. 3.—EFFECT OF LIVER (SINGLE BARBED ARROW) AND LIVER AND IRON (DOUBLE BARBED ARROW) IN DIMORPHIC ANAEMIA AND NUTRITIONAL MACROCYTIC ANAEMIA.

of which partly responded to anazhaemin and then to iron NAPIER (1940) in reviewing extensively the question of anaemia in pregnancy, stated that the macrocytosis of one deficiency might become masked by the microcytosis of the other and that many cases showed a combined deficiency NAPIER in his review pointed out that many reports by others of nutritional macrocytic anaemia had a low C.I. and were probably complicated by iron deficiency like those of FAIRLEY *et al* (1938) in Macedonia

HARE (1939 1940a & b) has surveyed the question of anaemia on the tea-estates of Assam both in the male and the non pregnant and pregnant female especially the latter His valuable contribution was in the nature of a survey and did not include investigation of the bone marrow of the test meal of the jaundice or of the response to treatment Blood counts the M.C.H. the M.C.V. and the M.C.H.C. were investigated It is not quite clear exactly how he divided his cases but the chief factor seemed to have been the mean corpuscular haemoglobin (M.C.H.) giving hypochromia, orthochromia and hyperchromia (which differs considerably from these three terms as defined in relationship to M.C.H.C.) An anaemia was judged to be microcytic if the M.C.V. lay below  $85 \text{ c } \mu$  (a high figure I submit) and normocytic if M.C.V. lay between 85 and  $120 \text{ c } \mu$  (the latter being a very high figure) and macrocytic if over  $120 \text{ c } \mu$  The normocytic group appears to have been divided into first a normocytic hypo-orthochromic group which showed itself by an absence of anisocytosis in the stained films together with an absence of nucleated reds and secondly, a micro-macrocytic hypo-orthochromic group (M.C.V. 87 to  $147 \text{ c } \mu$ , M.C.H. 15.59 to 29.66, M.C.H.C. 15.49 to 29.91 per cent) distinguished by marked anisocytosis with many macrocytes but few microcytes and a relative frequency of nucleated reds Since no details are available of the Price-Jones curve, or of a definition of 'marked anisocytosis' or of microcytes and macrocytes the haematological boundaries of this group appear to me to be open to much objection He believed that it was a new clinical entity but macrocytic hypochromic anaemia [M.C.V.  $>96.093 \text{ c } \mu$ , M.C.H.C.  $<28.17$  per cent (PRICE-JONES VAUGHAN and GODDARD 1935)] occurred in his normocytic micro-macrocytic and macrocytic hyperchromic groups His new clinical entity of micro-macrocytic anaemia appears to me to be open to grave objections although his views of the dual deficiency I consider correct

Possible cases of this dual deficiency anaemia have been reported in Great Britain and America Thus DAVIDSON (1941) recorded two cases (Group III Cases 1 and 2) which required both iron and liver before the anaemia, caused by a poor diet due to poor economic circumstances responded ISRAELS (1941) found the bone marrow in some of his malnutrition cases (no details given) showed signs of a megaloblastic change and of iron deficiency In America so-called atypical cases of chlorosis which only responded well when the iron was supplemented by liver have been recorded by ORDWAY, GORHAM and

ISAACS (1937), and MINOT (1937) has also seen cases. FAIRLEY (1940) possibly recorded a case of anaemia due to this dual deficiency for he reported the case of an Indian in London having a haemolytic hypochromic anaemia with gross splenomegaly which reacted to iron and crude liver extract.

In a recent review of 103 cases of macrocytic anaemia in pregnancy MUDALIAR and MENON (1942) report on their findings in Indian women. They record that thirty three cases had macrocytic hypochromic anaemia (mean corpuscular volume  $>85 \text{ c}\mu$  mean corpuscular haemoglobin  $<30\gamma\gamma$ ), and considered that this was evidence of a dual deficiency ankylostomiasis being in their opinion, largely responsible for the iron deficiency. They also recorded six cases of macrocytic hypochromic anaemia which, when given iron, changed into macrocytic anaemia. They considered that nutritional macrocytic anaemia (their macrocytic hyperchromic group) might have started as microcytic hypochromic anaemia, and changed into macrocytic hypochromic anaemia and then into macrocytic hyperchromic anaemia. Although they employed rather a different definition of macrocytic and hypochromic from that employed in this article, it is clear that they were sometimes dealing with a dual deficiency.

One aspect of the problem which has been inadequately investigated is whether microcytic hypochromic anaemia contains a masked deficiency of nutritional macrocytic anaemia. On the other hand, certain writers, like BEATRICE RUSSELL (1941) suggest that many cases of nutritional macrocytic anaemia, seen in West African pregnant women may contain a masked iron deficiency and that the colour index drops during liver therapy until therapeutic iron is needed to complete the cure.

#### THE INTERPRETATION OF THE RESULTS OF THE PRESENT SERIES

It is considered that many of the anaemias seen in Uganda natives showed two deficiencies. One is clearly that of iron deficiency shown by low values of the mean corpuscular haemoglobin concentration (MCHC.) and by hypochromia in the stained film and by the response to therapeutic iron. It is also considered that the bone marrow changes were distinctive this has been the subject of a previous communication. The other deficiency appears to be very similar to if not identical with, that present in nutritional macrocytic anaemia. The latter deficiency may be a single deficiency or it may be due to a group of allied deficiencies of the pernicious anaemia type, and cannot be defined with precision at the present time. The latter deficiency (or deficiencies) causes high values for the mean corpuscular volume (MCV) and anisocytosis, orthochromic cells together with megaloblasts and normoblasts in the stained film. Since the two deficiencies distort the blood picture in two different directions it is possible that the presence of those two deficiencies may not be reflected in any change of the colour index, or of the mean diameter (MD) or of the mean corpuscular haemoglobin (MCH).

The only purpose of this paper is to stress the fact that two deficiencies

occur even when least suspected. It is not proposed to discuss at length how these deficiencies arise for the facts necessary to the argument are not to hand. Our knowledge of whether nutritional macrocytic anaemia is a single pathological entity or a group of allied anaemias is at present incomplete. If it is proved to be dietetic in origin then it will be necessary to consider how far a dietetic deficiency of extrinsic factor was present in these cases. At present this can neither be affirmed nor denied because there have been scarcely any estimations of the amount of extrinsic factor present in various African articles of food. If it is proved that there is a temporary deficiency of intrinsic factor in nutritional macrocytic anaemia, as some have suggested (but none have proved) then it will be necessary to see if this is present in our cases in Uganda. Other factors may influence the absorption and utilization of the pernicious anaemia factor.

It is probable that any regeneration of blood necessary to compensate for the chronic haemolysis of malaria or the chronic intestinal haemorrhage of ankylostomiasis, may require increased supplies of the pernicious anaemia factor especially if this is lost from the body or otherwise destroyed in these or other diseases.

Concerning the iron deficiency present in this dual deficiency, our knowledge rests on a much more secure foundation. The iron content of many tropical foodstuffs is known, nutritional iron deficiency anaemia has been extensively studied in temperate climates and its relationship to chronic intestinal haemorrhage occurring in hookworm disease is fairly adequately understood.

#### TREATMENT

The treatment of the dual deficiencies in this anaemia presents problems far from solution at the present time. In addition, many cases in this series were tried on new liver fractions, some potent, some otherwise. The main points appear to be as follows but may be modified by subsequent observations.

Blood-destroying diseases should be vigorously attacked. malaria needs quinine which will give a reticulocyte response and a rise in the blood count which appears to depend on the following factors: first the intensity of the anaemia, and secondly the degree to which that anaemia was caused by malaria. Almost no response may be obtained in light infections. Hookworms are better left until the haemoglobin has regenerated to half, then the dangerous anthelmintics can be repeated until ova are absent or scanty.

Both deficiencies should be corrected from the very beginning and then blood regeneration is extremely rapid. This, however, does not demonstrate the dual deficiency. If deficiencies are corrected separately and the first reticulocyte response has subsided after correcting the major deficiency, then the correction of the minor deficiency causes a second reticulocyte rise dependent on the amount of haemoglobin present and on the intensity of the second deficiency. Cases in which one deficiency predominates may show scarcely any

response if the minor deficiency is first corrected but a large response to the correction of the major deficiency and in such cases it may be impossible to demonstrate the dual response. However if the major deficiency is corrected first, and no treatment is afforded to the minor deficiency blood regeneration, which is at first very rapid usually later becomes slow or even stationary at sub-optimal figures, and the blood picture becomes more and more that of the uncorrected deficiency. Thus if in macrocytic hypochromic anaemia iron is given the blood picture tends to change into that of nutritional macrocytic anaemia. Some of these cases might continue to recover even if liver were never given, but perhaps the elaboration and absorption of the liver principle from the diet is adequate to the occasion, and after a struggle the blood count may slowly rise to a normal figure.

The cure appears to be permanent if blood-destroying diseases are reduced to ineffective levels and the diet remains adequate but observations on this point are of necessity very inadequate.

In treating the deficiency of the liver principle, marmite (50 grammes daily) was adequate in two cases. Liver was more effective half a pound of cooked liver was usually adequate and was the method of choice among poor patients. It was cheap and it corrected many different deficiencies in the nutrition. Poor peasants eat this amount daily. Liver injections were more reliable more effective and more speedy. Some liver injections used in pernicious anaemia appeared to be ineffective or feeble or uncertain in the correction of this deficiency. Crude extracts are to be preferred, being always cheaper and are constantly effective thus liver extract for injection (B D H) 10 to 20 c.c. weekly campolon 10 to 20 c.c. weekly were always effective. Pregnancy may demand a large increase in the dose. Intercurrent infections including malaria, or serious disease may inhibit partly or completely all regeneration.

#### CONCLUSION

On the foregoing it is submitted that a dual deficiency was operating in many anaemias seen in the natives of Uganda. Whether iron deficiency should now be recognized as including the deficiency of the liver principle or nutritional macrocytic anaemia should be extended to include much iron deficiency is a question which will have to be decided. It is submitted, albeit with some hesitation, that the creation of a new anaemia is the simplest solution. Since the blood film, bone marrow aetiology and treatment has two aspects, it is suggested that perhaps the term "dimorphic anaemia" will commend itself to other workers in this field.

If due to the exigencies of the war other published work has not been accessible to me, I trust that difficulties beyond my control will be deemed an adequate apology to those whose work or whose nomenclature for this disease may have been overlooked.

## SUMMARY

1 Anaemia in the tropics is usually regarded as secondary to some tropical disease such as the haemolysis of malaria and the blood sucking of hookworms, nutritional (tropical) macrocytic anaemia is a deficiency anaemia but is regarded as uncommon apart from pregnancy

2. Three hundred and eighteen cases of anaemia in Uganda were classified along these lines but many difficulties arose in the classification due to overlap between the groups.

3 The anomalies chiefly concerned treatment iron might improve cases of nutritional macrocytic anaemia and liver might improve the iron deficiency anaemia of hookworm disease

4 The above classification was therefore abandoned in favour of the following procedure —

(a) Define the deficiencies present.

(b) Ascertain if possible what factors in the diet and also what disease might give rise to these deficiencies (e.g., hookworms accentuating an iron deficiency in the diet) or might destroy blood (e.g., malaria)

(c) Ascertain what associated infections or diseases might impede blood regeneration (e.g., tuberculosis, nephritis)

5 To indicate what deficiencies were present cases were classified by mean corpuscular volume (M.C.V.) and mean corpuscular haemoglobin concentration (M.C.H.C.) 134 cases were thus classified as —

I 27 cases of macrocytic orthochromic anaemia (nutritional macrocytic anaemia)

II 63 cases of macrocytic hypochromic anaemia.

III 27 cases of normocytic hypochromic anaemia

IV 5 cases of microcytic hypochromic anaemia (pure iron deficiency)

V 11 normocytic orthochromic and one microcytic orthochromic (mixed aetiology)

6 Cases which were in Groups II and III showed signs suggestive of a mixture of nutritional macrocytic and iron deficiency anaemias. The majority were cured by iron and liver, in others the response to these was tested separately

7 A detailed analysis of these two groups is given

8. In some of these cases both deficiencies appeared severe and needed treatment by iron and liver, which, given separately, induced a double reticulocyte response

9 In others one deficiency predominated and obscured the other and cases appeared to recover albeit slowly, if the major deficiency alone was corrected. The mechanism here is not understood, and it is not clear if they should be regarded as suffering from a dual deficiency. Much would, theoretically at least, depend on the diet received while the major deficiency was corrected, and whether curable intercurrent blood-destroying diseases were checked

10 No attempt is made to define clearly how these deficiencies arose,

but it is suggested that a dietetic deficiency of iron and the presence of hook worms accounted for the hypochromia and that the liver principle deficiency is nutritional macrocytic anaemia

11 The dual deficiency group might be classified as —

(a) Iron deficiency anaemia complicated by nutritional macrocytic anaemia

(b) Nutritional macrocytic anaemia complicated by iron deficiency

(c) A new clinical entity Since the peripheral blood, more particularly the blood smear shows two aspects the bone marrow shows different types of erythropoiesis and two factors have been detected in its aetiology and in its treatment, it is thought that the term "dimorphic anaemia" may commend itself to other workers more particularly those who have already described this anaemia in Indian pregnant women.

## REFERENCES

- DAVIDSON L. S. P. (1941) *Lancet* 2 171  
 FAIRLEY N. HAMILTON (1940) *Trans R Soc trop Med Hyg* 34 173  
 ——— *et al* (1938) *Ibid* 32 132  
 HANE, K. P. (1939) *Indian med Gaz* 74 467  
 ——— (1940a) *Indian J med Res* 27 1041  
 ——— (1940b) *Indian med Gaz* 75 274  
 HERGENROTHER R. S. F. (1937) *E Afr med J* 12 210  
 ISRAELS M. C. G. (1941) *Lancet* 2 207  
 MINOT G. R. (1937) Cited in ORDWAY *et al* (1937)  
 MUTALLAR, A. L. & MINOT G. R. (1942). *J Obstet Gynaec* 49 234  
 NAPIER, L. E. (1940) *Indian J med Res* 27 1009  
 ——— *et al* (1938a) *Indian med Gaz* 73 385  
 ——— *et al* (1938b) *Indian J med Res* 26 541  
 ORDWAY T. GOSHAM, L. W. (1937) *The Diagnosis and Treatment of Diseases of the Blood* (Revised by R. ISAACS) New York p 131  
 PRICE-JONES, C. VAUGHAN J. M. & GOODARD, H. M. (1935) *J Path Bact* 46 503  
 RUSSELL, BEATRICE A. S. (1941) *Lancet* 2 797  
 TROWELL, H. C. (1939) *E Afr med J* 15 402  
 ——— (1940) *Ibid* 17 14 & 80  
 ——— (1941) *Lancet*, 2, 303  
 ——— (1942) *Trans R Soc trop Med Hyg* 36 151  
 ——— (1943) *Lancet* 1 43  
 VINT F. W. (1939). *E Afr med J* 14 293

## INTRODUCTION TO THE STUDY OF TSETSE FLY REPELLENTS IN THE FIELD OF VETERINARY SCIENCE

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### PRELIMINARY REMARKS.

1 Many substances have been tried and some are in daily use in various parts of the world for the purpose of protecting cows from irritation by flies during milking time. To achieve success in this direction is not difficult, for the time during which the substance must be effective is a matter of no more than an hour or two, nor is it important if an occasional fly does break through the barrier of protection. An efficient tsetse repellent, however, must not only be effective for at least 24 hours, and preferably much longer, but during this time it must be practically 100 per cent. effective, since even an occasional fly breaking through the barrier may transmit death-dealing trypanosomes. The substance should also be cheap, non-toxic to mammals, and easily applied in the form of a dip or spray. Of these properties, cheapness is the least important to the experimentalist; the really important thing is to discover something that is protective and non-toxic, then demand will certainly make for cheapness through improvement of formula and by mass production.

2. Many suggestions regarding protection of stock from tsetse bites by means of repellents have been put forward, but none is founded on successful experience with animals, nor has any been adopted as the basis of a measure



now proved by experience to be of value. Although our own examination of a large number of substances for tsetse repellence has met with little success, yet as the work has been carried out systematically for more than a year during which time many improvements in technique have been made we believe our experience can serve as a useful introduction to later and, we hope more successful experimentation of the same kind.

3. The percentage of tsetse-flies that harbour trypanosomes infective to stock varies with circumstances but dissection of a hundred or more tsetse from any locality usually discloses between 5 and 10 per cent with trypanosomes in the hypopharynx, and such tsetse are nearly always infective to stock. The percentage is sufficiently high to make it necessary that a repellent, to be effective should stop all tsetse biting during the time protection is required.

4. But even more than this may be required. Apparently the delicate proboscis remains ensheathed in the protecting palpi which project horizontally in front of the tsetse's head at all times except when it is lowered for the definite purpose of feeding. On these occasions, if the tsetse is infective trypanosomes are ejected immediately the proboscis punctures the skin or probably even as soon as the skin is touched firmly. Dr ERIC BURTT of Tinde Laboratory for the Study of Human Trypanosomiasis, has been paying much attention to the numbers of trypanosomes extruded on to a glass slide when this is interposed between the proboscis of a hungry infective fly and a guinea pig which the fly is straining to reach. In the course of a minute's probing, several hundred trypanosomes may be extruded. This is important, because we found that hungry flies applied to a portion of skin on which a repellent had been sprayed might probe even when they did not actually feed—and by feeding we mean the imbibition of sufficient blood to give a transitory red tinge to the anterior part of the abdomen. By engorgement, we mean full distension of the abdomen.

5. To ascertain if probing without subsequent feeding might infect, one of us went to Tinde, where individual tsetse known to be infective were kindly placed at our disposal by Dr BURTT. There five rats and one young ant-bear were dressed with an appropriate repellent. Subsequent feeding tests with clean flies were carried out until—after about 48 hours—the stage was reached when hungry tsetse might be expected to probe without feeding. Four separate flies, known to carry *Trypanosoma rhodesense* in infective form, were then applied to the rats and ant bear—one to each of three rats, and one at intervals, to two rats and the ant bear. In all cases the hungry flies probed actively but only in the case of one rat did the fly actually feed. nevertheless all six animals showed trypanosomes in their blood a week later. Thus excluding the rat on which a fly fed, all the experimental animals—four rats and an ant bear—were infected by tsetse that probed without definitely feeding.

6. From what has just been said it may be gathered that to keep tsetse from feeding may not be difficult, but to keep them from probing is extremely

difficult. Actually if we thought that what occurred at Tinde with rats and captive flies would also occur in the field with cattle and wild flies we should feel despondent regarding the chance of any satisfactory repellent being discovered. But the two sets of conditions are different. In the first place wild flies do not behave exactly like captive flies which are tame by the time they have reached the stage of being infective, and when hungry they do not hesitate a moment after being applied to a tasty host before probing to find a suitable spot for obtaining blood. A wild fly on the other hand, rarely bites immediately it alights, it takes stock of its position first. Now the only kind of repellent likely to be successful is one that is absorbed through the pulvilli of the feet and rapidly causes paralysis or death, therefore if a fly in contact with such a substance does not start to feed almost at once there is a good chance it will not start at all. Hence a repellent that fails to stop infection when conditioned captive flies are applied to a rat, will not necessarily fail to protect domestic stock in the field.

7. In the second place the rat (and presumably the young ant bear) is particularly susceptible to infection with *T. rhodesiense*, and the Minimal Infective Dose is therefore proportionately small. But although data are not available to confirm the supposition, it is reasonable to suppose that the M.I.D. of trypanosomes is much greater for the ox than it is for the rat, and that light probing, which would find a blood vessel in a rat's skin and transmit an infective dose of trypanosomes, might fail to harm an ox.

8. The point we wish to make is that when a substance is being tested for tsetse repellence one can feel confident about its efficacy if throughout the prescribed time, it stops all tsetse from probing. If though, some of the tsetse probe even though none of them feeds, the substance may or may not be effective, and the doubt can only be resolved by further experiments, this time under field conditions. So far we have not found any harmless substance that will certainly stop hungry flies from probing throughout 24 hours, and only one that will stop them feeding—and even this partial success was obtained with donkeys but not with cattle.

#### NOTES ON TECHNIQUE.

9. All laboratory trials were carried out with captive *Glossina morsitans*. The pupae collected by skilled natives in a dense fly belt near Kondoia Irangi, were taken to a resident official, who tied them in a little muslin bag, packed this in cotton wool within a small wooden box, and despatched them to us by post. At Mpwapwa they were transferred to a jam jar, the mouth of which could be closed by a piece of mosquito netting held in position by an elastic band. The layer of live pupae should not be more than about an inch deep, or emerging flies may not be able to work their way from the bottom. As the flies hatched they were put into Bruce boxes to the number of about 50 in each box, and without regard to sex. Bruce boxes are rectangular boxes

6 in.  $\times$  4 in.  $\times$  3 in. wooden except for the two largest sides, which are made of fine wire netting one end has a hinged door and the other is pierced by a hole closed by a wooden plug. The boxes were kept away from direct sunlight on a bench within a fly proof room. They were placed on large mesh wire netting stretched over shallow trays containing a little water. Stock flies not required at once were given a chance every day to feed on a healthy sheep.

10 Hungry flies for test feeds were obtained as follows. After a box of stock flies had been applied for about 10 minutes to the clipped side of a healthy sheep the insects were shaken into a bag of mosquito netting 2 ft.  $\times$  1 ft. in size and all the engorged flies were picked up with the aid of a dry test tube and transferred to an empty Bruce box. This was labelled to show the number of flies and the date of feeding. After 3 days without food they were put into glass jam jars closed by clean netting. From five to eight flies were put into each jar which was then put mouth down on the wire netting. After another 24 hours *i.e.* when the flies had been just 4 days without food, they were ready for test feeding. About six is a good number for each jar it is small enough to permit observation of individual flies, and large enough to give each test the chance of being fully valid. Repellence was considered significant if not more than one fly in any one bottle fed on the test animal, during the time that not less than half the flies in another bottle applied to a control animal of the same species as the test one became engorged. As stated above repellence was considered as *probably effective* if no flies fed on the test beast. It would have been considered *definitely effective* if no flies probed.

11 Many pitfalls have to be guarded against. Bottles and gauze covers must be chemically clean. Captive flies are extremely sensitive to even such traces of poison as may be introduced by an assistant cleaning jars with sand collected near a chemical laboratory or failing to wash well and afterwards to rinse most thoroughly all gauzes used previously in tests with substances toxic to flies. Tsetse in such a contaminated jar may show no sign of illness beyond anorexia detectable if they are applied to a control animal but leading to a false conclusion if they are applied to a test beast. We found it inadvisable too to make test feedings in the open air. Healthy flies in clean bottles may be deterred from feeding even on clean animals by the mere change from indoors to outdoors. In all our later tests, therefore the animals were brought into a loose box in the same building as the room where the flies were housed, and under these circumstances it was seldom at any time of the year that the stipulated 50 per cent. or more of control flies did not engorge in the 6 minutes allotted for the application of each jar. It is advisable, of course, to use quiet animals which are easily handled.

12 At one time we thought there might be an objection to the use of glass jars at all seeing that these retain the moisture given off by the skin, and with it any exhalation arising from the drug used. Therefore we carried out parallel tests with flies in (a) glass jars, and (b) cages of mosquito gauze

stretched over a basket frame. The results on a series of successive days were as follows —

TABLE.  
COMPARISON OF GLASS JARS WITH GAUZE BASKETS.

Date	Flies Fed on Test Animals.		Flies Fed on Controls.	
	Glass Jars.	Gauze Baskets.	Glass Jars.	Gauze Baskets
14th January	0/6	0/6	4/6	4/6
15th	2/7	2/7	3/6	5/7
16th	3/10	1/9	3/9	0/8
17th "	0/15	0/14	6/14	6/14
18th "	0/8	0/13	3/13	8/13
19th "	0/11	0/13	4/13	8/13
20th	0/7	0/6	7/7	3/6
21st "	0/7	0/7	5/7	5/7
22nd "	1/8	4/7	7/8	0/7
	6/79	7/82	41/83	45/81

12. The table shows the number of flies applied and the number that fed in each test, and although certain anomalies are apparent, as the tests were made before the need for all the precautions described above had been recognized nevertheless the results as a whole show that little error is introduced by the use of glass jars — therefore as these are more convenient than gauze baskets and permit the flies to be watched during tests they are recommended for use. A small point about their construction is that the inner surface of the neck should continue flush to the brim — if it curves outwards flies near the circumference are liable to be nipped and damaged when the mouth of the bottle is pressed against an animal.

13. Another point that arose was whether the presence of gauze was not responsible for flies acting differently from their behaviour if they lighted on the skin. To test this we applied jars and withdrew the gauze immediately so that the tsetse could fly straight on to the hair. This made no difference to the percentage that fed but as might be expected, there was less probing of a strongly treated skin when there was no gauze. Nevertheless there was some brief probing even when the concentration of repellent was so high that contact for only a minute or two caused the fly's death a short time afterwards.

#### Summary

14. Summing up these remarks on technique. We advocate the use of chemically clean gauze-covered glass jars containing about six tsetse that

have been starved for 4 days, as a useful unit for testing fly repellents. The hungry flies should not be taken out of doors for their feeds but the animals should be brought indoors to the flies.

### PROCEDURE.

15 The procedure of testing any substance in the laboratory is a series of steps —

(i) The compound is applied to a small clipped area of the skin of a housed sheep. After 24 hours, hungry tsetse in one or more gauze mouthed jars are applied for 6 minutes, and a note is made of their behaviour and particularly of the number that feed. If not more than one fly in any jar feeds, there is significant repellence and the second step is taken.

(ii) An ox which lives out of doors all day is used. Again only a limited area, but this time of unclipped skin, is treated with the compound. After 24 hours the animal is brought into the fly-house and while some flies are applied to the treated areas, others are put on controls or on untreated portions of the skin of the test animal. The criterion of significant repellence used in the first step is again accepted, and if in addition, there is no sign of local irritation the third step is taken namely

(iii) The application of the compound to the whole surface of an ox or donkey by spraying or hand washing to test its toxicity. If no symptoms develop, then as a final step

(iv) The substance is submitted to comprehensive tests to get as much information as is obtainable without field trials. So far only one substance—pyrethrum—has reached this final stage of testing

### SUMMARY OF UNSUCCESSFUL REPELLENCY TESTS.

16. Altogether more than 140 different substances and mixtures have been tested without success for repellent action against tsetse-flies, using the procedure outlined above. For convenience they have been grouped below into (1) pure inorganic reagents, (2) pure organic substances (3) oils, (4) extracts, (5) miscellaneous substances, and (6) mixtures of two or more substances. As would be expected, most of these substances had no repellent action on tsetse, and to economise space notes are added after each group drawing attention to anything of interest. The complete list of substances tested is given, however, because there is such lack of information on this subject in the literature. Unless otherwise indicated, all tests of single substances were made with 2 per cent. aqueous preparations.

#### (1) Pure Inorganic Reagents.

17. 1 per cent. ammonium carbonate, antimony trichloride saturated boric acid solution, bromine, cobalt nitrate, 1 per cent. copper sulphate, ferric perchloride, 1 per cent. iodine in potassium iodide solution, 0.1 per cent. mercuric chloride, potash alum, potassium bromide, potassium chromate, potassium ferrocyanide, potassium thiocyanate, 1 per cent. sodium fluoride, sodium nitroprusside, sodium thiosulphate, sodium tungstate, powdered sulphur, 1 per cent. zinc sulphate.

18. These inorganic reagents were without appreciable repellent value and in most cases flies fed as well as if no chemical had been applied.

(2) *Pure Organic Substances*(a) *Aliphatic Compounds*

19 Acetic acid, acetone, alanine, ammonium oxalate, amyl alcohol, carbon disulphide in soapy water, carbon tetrachlorethylene in soapy water, carbon tetrachloride in soapy water, citric acid, furfural, glycerin, 1 per cent. hydroxylamine, 1 per cent. iodoform suspension, lactic acid, 1 per cent. lead acetate suspension, secondary octyl alcohol, oxalic acid, potassium antimony tartrate, sodium di-ethyl di-thio-carbamate in acetone water, sodium malonyl urea, sodium potassium tartrate, 1 per cent. sodium taurocholate, tartaric acid, 1 per cent. thiourea, urea, uric acid in dilute alkali, zinc acetate.

20 Sodium malonyl-urea and uric acid both showed a slight repellent action but not enough to make them of practical use. On the other hand, potassium antimony tartrate showed little repellent action but killed a high percentage of the flies. Carbon disulphide was appreciably repellent when applied to animals indoors but proved to be too volatile for use when exposed to the sun's rays. Urea appeared actually to attract the flies.

(b) *Aromatic Compounds*

21 Acetanilide 0.1 per cent., acriflavine 0.5 per cent., 7-amino-9-p-amino-phenyl 10-methyl-phenanthridinium chloride, aniline, aniline acetate, benzaldehyde, benzene emulsion, benzinide in alcohol water, benzoic acid, brucine in dilute acid, camphor in alcohol water, 1 per cent. cholesterol in acetone water, 1 per cent. cresol, 4:4 diamidino diphenyl ether dihydrochloride, 4:4 diamidino diphenyl ether propane dihydrochloride, 4:4 diamidino stilbene dihydrochloride, 2:4 dinitrophenol in acetone water, p-dichlor benzene in acetone water, saturated diphenylamine, guaiacol, hexamethylene tetramine, 8-hydroxy-quinoline in alcohol water, menthol in acetone water, methyl orange in alcohol water, methyl salicylate, naphthalene in hot alcohol water,  $\alpha$ -naphthol, nicotine sulphate, 1 per cent. nitrobenzene, 0.5 phenol, phenothiazine, in phenylene diamine in acetone water, saturated picric acid, pyridine, pyrogallol, quinine in dilute acid, quinol, resorcinol, 0.4 per cent. rotenone in acetone water, saponin, sodium  $\beta$ -naphthoquinone sulphonate, strychnine in dilute acid, sulphanilic acid, tannic acid, tartrazine in alcohol water, thymol, catechol, xylene.

22 Whilst a number of these aromatic compounds caused a small reduction in the number of flies that would feed on housed sheep, very few showed sufficient repellent action to justify more tests on animals exposed to the sun. Compounds such as aniline acetate, benzaldehyde, thymol and rotenone all failed under the more severe tests out of doors. Nicotine sulphate had good repellent and killing action on tsetse but Step 11 showed it to be extremely toxic when applied to the whole animal. (See HORNBY & FRENCH, 1942.)

(3) *Oils*

23 Almond, aniseed, castor, 5 per cent. cedarwood, chaulmoogra, chenopodium, citronella, clove, coconut, cod-liver, cotton-seed, eucalyptus, linseed, neatfoot, olive, peppermint and tagetes oils. Also 20 per cent. emulsion of a proprietary eucalyptus "fly blow" oil, 5 per cent. used engine oil, 5 per cent. kerosene, paraffinum liquidum and oil. picea rect.

24 None of these oils gave satisfactory repellence. Eucalyptus oil gave promising results on animals kept indoors but this promise was not fulfilled when the animals were exposed to the sun. Very disappointing results were obtained with citronella oil which, after 24 hours, completely failed to show repellent action. GRAYBILL (according to AUSTEN & HECH, 1922) states that fish oil is rated as one of the best fly repellents but in our series cod liver oil afforded no protection against tsetse. From the same source we learnt that BAKER found a mixture of kerosene, fish oil and citronella oil emulsified with milk and diluted with water was a good repellent against *Lyperosia* and *Stomoxys* but in the *Mpwapwa* tests the mixture did not give promising results.

(4) *Extracts*

25 Ether and acetone extracts of herbs equivalent to 2 per cent. powder in kerosene soap emulsion, hot aqueous extract of fresh *Ocimum americanum* leaves, hot aqueous extract

soft soap solution, 5 per cent. and 10 per cent. extracts of wattle bark

26 The leaves of the two local wild plants possessed pronounced odours, and it is said that natives sometimes place bunches of *Ocimum* leaves near their heads when they go to sleep to keep off mosquitoes. Neither of these aqueous extracts was of any value against tsetse. The extracts of *detras* had poor repellent powers.

#### (5) Miscellaneous Substances

27 2 per cent. tincture of safoetide saturated solution of cochineal, beechwood creosote, 1 per cent. and 2 per cent. suspensions of *detras* powder in soapy water, cattle dip containing 0.16 per cent. arsenious oxide, Friar's balsam, Jeyes fluid, Stockholm tar.

28. In spite of the fact that SIMMONS found beechwood creosote to be one of two substances (the other being beechwood oil) which would repel tsetse when smeared on natives it had no value as tested by us. Tar emulsions also proved quite useless. *Detras* powder suspended in soapy water gave a small repellence when sprayed on oxen grazing, even in the sun, but the results were very variable and emphasized the difficulty of spreading powders evenly over the whole body surface.

#### (6) Mixtures of Substances

29 Cattle dip with nicotine sulphate, naphthalene-kerosene emulsions, naphthalene-used engine oil emulsions, nicotine sulphate-wattle extract suspensions, nicotine sulphate-kaolin suspensions, nicotine sulphate-tar-oil pacts rect. emulsions, 10 per cent. oil, pacts rect. in cod-liver oil.

30 The toxicity of nicotine sulphate could not be reduced to a safe level, though wattle extract did appear to have some value for this purpose. Cattle dip (sodium arsenite) had no influence on the repellency of any substance to which it was added.

### PYRETHRUM AS TSETSE REPELLENT

31 Literature on pyrethrum and pyrethrins is voluminous, yet neither Mr. W. H. POTTS, who kindly aided us in our search, nor ourselves could discover more than one reference to tests of this drug against tsetse. This reference, in a report inaccessible to us, was by HARRIS (1930) who found that extract of pyrethrum brought about paralysis of the locomotor centres of the insect when the pulvilli of its feet came into contact with the drug, the fly recovering or succumbing according to the strength of the preparation.

32. We shall not give details of the long series of observations made by us when we used, first, pyrethrum powder, then home made extracts of this powder, then a concentrated oleo-resin of known pyrethrin content kindly prepared for us by Mr. V. A. BECKLEY of the Scott Agricultural Laboratories, Kenya, and finally "pyagra," a well known proprietary preparation. With all we got results that were tantalizingly within measurable distance of success, and yet always fell short of the minimum we desired.

33 Applications of (a) 2 per cent. pyrethrum powder suspended in soapy water, or of (b) diluted home-made ether or kerosene extracts of powder equivalent in pyrethrin content to (a), or of (c) dilutions of the Kenya preparation so that the spray contained 20 mg. pyrethrins per 100 c.c. or of (d) 2 per cent. pyagra—all passed tests represented by Steps i, ii and iii of the procedure outlined on page 48. It was the observations that constitute Step iv which showed that the great drawback to pyrethrum is the destruction of its active

principles by sunlight. It became clear that these pyrethrum preparations were harmless to the animal even when applied to the whole surface on 5 or 6 successive days. It was also obvious that they would keep any tsetse from biting—though not necessarily from probing—for more than 24 hours if the animal was kept indoors but that the same degree of protection could not be relied upon if the animal was exposed to bright sunlight.

34 We need not describe our attempts to get better results in the following ways: (1) The addition of oils such as castor oil, cotton-seed oil, coconut oil, lanolin, used engine oil, and tagetes oil, or of anti-oxidants as thymol, pyrocatechol, and hydroquinone, or of insecticidal adjuvants as naphthalene, and arsenic. (2) Increasing within reasonable limits the pyrethrin content of the spray. (3) Endeavouring to get a cumulative effect by five or six applications on successive days. All were failures and in the end we decided that as good a tsetse repellent as any other we could produce was a simple 2 per cent. emulsion of pyagra (a proprietary pyrethrum extract sold for household use against mosquitoes and flies).

35 The emulsion should be prepared just before use, and be made by first adding 60 c.c. of pyagra to 300 c.c. of 2 per cent. soft-soap solution, and then adding water to make a total of 3 litres, stirring all the time. This is sufficient for the thorough spraying or washing of a donkey or ox that does not weigh more than 7 or 8 cwt.

36 The emulsion is alkaline in reaction, a condition unfavourable to the stability of pyrethrum, but any advantage derived from neutralizing or acidifying the preparation did not appear to warrant the extra trouble—and if a preparation is to be made up daily in the field, the simpler it is the better. We shall describe these particular tests in some detail, as they show the kind of result to be expected when 2 per cent. pyagra is used as a tsetse repellent.

37 The simple 2 per cent. emulsion made with laboratory tap water was alkaline and required 6.2 c.c. of N/10 HCl per litre to neutralize it, using phenolphthalein as indicator.

23.4.42.—We made three preparations: (a) Ordinary alkaline emulsion; (b) emulsion made neutral by adding 6.2 c.c. of N/10 HCl per litre; (c) emulsion made acid by adding 12.4 c.c. of N/10 HCl per litre. At about 9 a.m. Ankole heifer No. 114 and a Catalonian grade donkey were sprayed with (a). Ankole heifer No. 108 was sprayed with (b) and Ankole heifer No. 107 with (c). They were then turned out to graze with the rest of their herd of heifers and donkeys. During this day the Relative Humidity (R.H.) at 2 p.m. was 50. Maximum Shade Temperature (M.S.T.) was 28.5°C. and there were 8 hours 25 minutes of sunshine.

24.4.42.—At about 9 a.m. i.e. after 24 hours the animals were brought into the fly-house for testing and a jar of hungry flies put on to the loin of each.

On heifer 114 sprayed with (a), 2/5 fed.

" the donkey	"	(a)	0/6	"
" heifer 108	"	(b)	0/7	"
" 107	"	(c)	0/8	"
" control heifer	"		4/5	"

The animals were then turned out again. On this day R.H. was 71. M.S.T. 25.8° sunshine 3 hours 25 minutes and there was a trace of rain.



29.3.42—After 72 hours.

On donkey 8, jar applied to shoulder 0/8 fed.

" control, " " forehead 0/8 "

" " " shoulder 4/6 "

This result of repellence after three days was so satisfactory that we decided to give the zebu or another chance. Accordingly on 3.6.42, we thoroughly swabbed a zebu ox and a donkey R.H. 35 M.S.T. 78 sunshine 7 hours.

4.6.42—After 24 hours

On zebu ox, jar applied to rump, 3/8 fed.

donkey jar applied to shoulder 0/8

donkey control, jar applied to shoulder 5/8

Some of the flies may have probed. All were affected some severely. If the result be compared with that obtained on, say 25.4.42, it may be inferred that washing by hand and spraying give the same results.

We were now satisfied that 2 per cent. pyagra would protect donkeys for more than 24 hours from being fed on by tsetse but it was also clear that hungry tsetse flies would probe even when they could not feed. This is clearly shown by the following experiment:

1.6.42—Donkey 8 was thoroughly swabbed with 2 per cent. pyagra at 3 p.m. After only 1 hour in the sun, at 4 p.m. four flies were applied and two probed, although all four were moribund before the jar was removed after the usual 6 minutes period. Slight poisoning is indicated by restlessness and vigorous clearing movements. More severe action causes inco-ordination. When fatally affected, the fly falls over on to its back lying thus for it may be hours or only minutes, before dying.

We wished to know if pyagra was strongly trypanocidal. If so it might thereby give some measure of protection against inoculation of trypanosomes by slight probing. Accordingly we made up a 1-1 000 pyagra emulsion in normal saline vigorously shaking the bottle all the time. To 10 c.c. of this fine emulsion we added 0.5 c.c. of rat's blood rich in *Trypanosoma rhodesense* and at once made a cover-slip preparation. All trypanosomes were dead by the time they could be put under the microscope. A control preparation of 0.5 c.c. of the same blood in 10 c.c. of normal saline showed active trypanosomes for many minutes. Thus 2 per cent. pyagra must exert a direct lethal effect on any trypanosomes with which it comes in contact.

Following this observation we dissolved 1 gramme of the Kenya oleo-resin—containing 400 mg. of pyrethrins—in 40 c.c. of sterile coconut oil, and injected it intramuscularly into a cow affected with *T. congolense* disease. There was neither general reaction nor serious local reaction. Trypanosomes were found subsequently at irregular intervals, and it is not clear whether there had been any appreciable in vivo trypanocidal action or not. The observation is only recorded to show the harmlessness of pyrethrum to mammals.

### PRELIMINARY FIELD TRIAL.

Through the courtesy of the Director of Veterinary Services we were able to accept the kind offer of Mr F. G. WADDINGTON Veterinary Officer to test the protective action of pyagra applied to donkeys passing through a fly belt.

On 13th October six donkeys left Singida to pass into the tsetse infested woodland to the east of the Rift Wall, before being brought back to Singida again. The journey lasted 7 days, and for five of them the donkeys were passing through country heavily infested with *Glossina morsitans*. Three of the donkeys were sprayed each morning with 2 per cent. pyagra emulsion, and three were left untreated as controls. The donkeys accompanied a porter *safari* of Mr WADDINGTON and he himself walked with the animals and noted their reactions to attacks by tsetse. He summarizes his observations as follows—

During 7 days *safari* the donkeys were in tsetse-infested country for

5 days and were known to be definitely exposed to the flies in large numbers during 3 of these days

The three treated donkeys passed through the tsetse quite undisturbed by them. Tsetse were seen to alight on the treated animals on several occasions, but they only remained on them for a few seconds and apparently did not bite

The untreated controls were seen to be bitten frequently and were constantly worried by the tsetse

The animals were known to be free from trypanosomes at the commencement of the journey and blood smears were taken every other day for 10 weeks after its completion. Only one donkey an untreated animal developed trypanosomiasis and he did not show parasites (*T. congolense*) until 14th December. The result of the trial is therefore promising without being conclusive

### SUMMARY

A technique was worked out whereby the action of any substance in repelling tsetse flies can be compared with that of pyrethrum which is the only one of about 150 substances that gave any promise of practical efficacy in the veterinary field

A freshly prepared emulsion containing 0.2 per cent pyrethrins can be applied with the utmost freedom to any animal without danger and it is probable that an animal so treated will not be fed upon by tsetse flies within the next 24 hours if it remains in subdued light

Direct sunlight however quickly reduces and eventually destroys this protective action. In the case of zebu cattle exposed to normal African sunlight, tsetse will feed within 24 hours of the drug's application. In the case of donkeys however complete protection against the feeding of tsetse during more than 24 hours can be obtained by spraying or washing with a pyrethrum preparation.

Many kinds of pyrethrum preparations were tried but in the end we found we could not improve on a freshly made emulsion consisting of 2 per cent pygra in weak (0.2 per cent) solution of soft soap

But although tsetse will not feed on a donkey sprayed recently with 2 per cent pygra or similar pyrethrum preparation they may probe and experiments with rats showed that this may be sufficient to set up infection. However reasons are given why one cannot argue directly from tame flies and white rats to wild flies and large domestic animals

A field trial gave inconclusive results because although the three treated donkeys remained healthy only one of the three untreated animals became infected. However while the controls were worried by tsetse the treated animals were apparently undisturbed by the flies

## CONCLUSION

A freshly prepared emulsion of 2 per cent. pyagra in weak soap solution, thoroughly swabbed or sprayed on to a donkey will prevent tsetse feeding during a period of more than 24 hours of any weather except, possibly heavy rain. If during this period, tsetse remain in contact with the skin for more than a few seconds they become seriously often fatally poisoned. Nevertheless, during the brief interval before the effect of the poison is felt, a conditioned hungry fly may probe and possibly infect. Whether wild flies would probe similarly and sometimes infect can only be ascertained by further field trials.

## REFERENCES.

- AUSTEN, E. E. & HIGGS, E. (1922) *Tsetse-flies their Characteristics Distribution and Bionomics*. London: Imperial Bureau of Entomology.
- HARRIS, R. H. T. P. (1930) Report on the bionomics of the tsetse fly (*G. pallidipes* Aust.) and a preliminary report on a new method of control, presented to the Provincial Administration of Natal. (Abstracted in *Rec appl Ent B* 19 (1931), 13.
- HOSBORN, H. E. & FLETCHER, M. H. (1942) Acute nicotine poisoning of cattle. *J S Afr vet med Ass* 13: 1-4.

## EPIDEMIC OF BERIBERI AMONGST SOMALI TROOPS IN EAST AFRICA COMMAND

BY

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An epidemic of beriberi amongst Army personnel is of interest because each man is receiving a standardized daily diet, which renders possible an estimation of his vitamin intake. The outbreak also deserves mention because no other cases of the disease have occurred in the East Africa Command. It is proposed first to give a description of the epidemic and then to discuss the various constituents of the Somali diet, comparing it with the food consumed in civil life.

*Description of Epidemic*—The first cases were seen during a medical inspection of the Somali Frontier Guards on 19th February 1942. There were nine patients.

*History*—The history varied from 4 to 25 days. All the patients complained of swelling of the whole body usually commencing in the legs. Other symptoms were dyspnoea, palpitation, numbness of legs or epigastrium and tiredness of legs after exertion.

### *Clinical Examination*

1 *Oedema* with pitting on pressure, most marked over the subcutaneous surface of the tibia, was present in seven of the cases. There was often swelling of the face and chest and, in one case oedema of the lungs as evidenced by a cough with blood stained sputum. There was no oedema of the scrotum. There was no albuminuria.

2 *Cardiac Signs*—Enlargement of the heart both to left and right, was present in four cases and was accompanied by signs of venous congestion such as distended cervical veins, epigastric pulsation and tachycardia with diminished exercise tolerance.

3 *Polyn neuritis*—There were patches of anaesthesia of varied distribution in four patients. The anterior surfaces of the knees and anteromedial surfaces of tibiae were usually involved. Other parts affected were the tips of toes and fingers, epigastrium, flanks and in one case, the left sternoclavicular joint. There was hyperaesthesia of calf and quadriceps muscles. There was considerable loss of power in the lower limbs, which in one case necessitated the

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support of an assistant on either side during walking knee and ankle jerks were absent in this patient. A characteristic feature was the symmetrical nature of the neuritic signs.

*Extent of Epidemic*.—An inquiry revealed that seven Somalis in another company who were on the same diet as these patients but who were stationed several miles away were suffering from identical symptoms. There was, however, no beriberi in a company of King's African Rifles situated 9 miles away nor were the five Somalis attached to this company affected presumably owing to the fact that beans were included in their diet.

*Therapeutic Test*.—Two of the patients were admitted to hospital. Each was given an intramuscular injection of 10 mg. of vitamin B<sub>1</sub> (betaxin).

One case was a typical wet beriberi with marked pitting oedema of legs, arms, chest and back. He had an enlarged heart with signs of venous congestion, and also showed patches of anaesthesia over knees, tibiae, flanks, and tips of fingers and toes. The injection resulted in almost complete disappearance of the oedema within a space of 4 days together with complete recovery from the venous congestion and a return of normal sensation.

The second patient was a severe case of dry beriberi with neither oedema nor cardiac symptoms but with advanced neurological signs. He had extensive anaesthesia of both knees and calves. He could not walk, or even stand without support. All deep reflexes were lost in the lower limbs. There was severe tenderness of his calves and quadriceps. The injection resulted in a marked improvement in the signs within 4 days, the muscle hyperaesthesia having almost disappeared and the areas of anaesthesia having greatly diminished in extent.

*General Treatment*.—A daily ration of  $\frac{1}{2}$  lb. maize meal which was the only available vitamin B<sub>1</sub> rich food at the station, was immediately prescribed. On my return from the inspection I recommended that a daily ration per man of  $\frac{1}{2}$  lb. of either ground nuts or beans should be dispatched to the unit. A supply of beans arrived 12 days later after my second visit.

*Course of Epidemic*.—A second visit was made to the S.F.G. 12 days later (on 3rd March). All the cases previously examined on 18th February had completely recovered with the exception of two patients who were much improved and who only showed signs of polyneuritis such as hyperaesthesia of calf muscles, weakness of legs and absent ankle jerks. There were two new cases of beriberi, oedematous and dry types respectively. The recoveries were attributed to the ration of maize meal and the onset of fresh cases to the fact that there was insufficient maize for prophylactic treatment of unaffected Somalis. The delay in recovery of two of the patients was set down to some anorexia on the part of these men who consequently did not consume their full ration of maize and to the fact that as is well known, polyneuritic signs often take much longer to respond to treatment than oedematous and cardiac symptoms. No more cases of the disease occurred.

*Cause of the Outbreak.*—For 6 months the Somali Frontier Guards had subsisted on the following daily rations: Rice 1 lb, fresh meat  $\frac{1}{2}$  lb, ghee 2 oz, dates  $\frac{1}{2}$  lb, sugar 2 oz, salt  $\frac{1}{2}$  oz, tea  $\frac{1}{2}$  oz. One orange was supplied per week. For the first two of these months no meat was available. An investigation revealed that Somalis of another unit in the same district, who received identical rations, did not suffer from beriberi. They had, however, only been limited to this diet for 2 months (the period of development of beriberi occupying a period of 80 to 90 days).

An examination of the above diet shows that there is a deficiency of aneurin. The table of Somali Diets (p. 59) gives the composition of the Army rations together with an analysis of those items, namely, maize meal, beans and ground nuts, which were recommended for prophylactic and therapeutic treatment. The composition of some articles of food taken by Somalis in civil life has also been included in order to demonstrate how some of the deficiencies in the Army rations are overcome by the native diet.

#### NOTES ON THE TABLE OF SOMALI DIETS

1. *Rice*—The thiamine and nicotinic acid values have been worked out from rice containing 28 per cent. pericarp. The amount of pericarp was determined by the method of VEDDER and FELICIANO (1928) i.e. 100 grains of rice are stained with Gram's iodine solution for 1 minute. The iodine having been rinsed off with water, each grain is examined and the amount of pericarp remaining expressed as a percentage. An examination of a sample of rice from the Somali diet gave a result of 28 per cent. pericarp. By applying this degree of polishing to standard figures for polished and unpolished rice, the aneurin (*Field Service Hygiene Notes* 1940) and nicotinic acid (LEONG 1940b) contents were estimated.

2. *Beef*—Calculations were made in conformity with the food estimations of the East Africa Command after deducting 22 per cent. for waste material. The vitamin A content is the amount present in 57.8 grammes beef fat. The thiamine and nicotinic acid figures were taken from beef boiled 10 and 20 minutes respectively in order that they might tally more closely with the vitamin content of the Somali food (for the meat of East African soldiers is usually cooked in the form of a stew).

3. *Ghee*—As no references (except for vitamin A) to the vitamin content of ghee could be found, estimations for butter have been inserted. Since some destruction of vitamin probably occurs during the preparation of ghee from butter, the figures may be over-estimations.

4. *Fruit*—The stated quantities of nicotinic acid in dates and orange are based on the average for the fruits examined by LEONG, who gave no specific figures for these foods.

5. *Maize*—The thiamine value is that for local maize which contains



135 international units per gramme (personal statement by Dr D HARVEY Biochemist, Medical Research Laboratory Nairobi) Bone meal is added to maize for East African troops in order to overcome the shortage of calcium.

6 *Beans*—The iron content was taken from French beans *Phaseolus vulgaris*, the riboflavin from *Cajanus indicus* and the nicotinic acid from *Vigna sinensis*. The other figures which were copied from the East Africa Command food values had been taken from FISEN and ROSCOE'S estimates for *Cajanus indicus*, *Cajanus cajan* and *Phaseolus* sp. in the case of vitamins A, B<sub>1</sub> and C respectively and from local analysis of Canadian wonder beans in the case of the energy yielding constituents.

7 *Ground Nuts*—The high vitamin B<sub>1</sub> value of 410 international units is present in  $\frac{1}{4}$  lb of raw peanuts but the aneurin content is considerably influenced by cooking as shown by the fact that baking reduces the figure to 268 and that boiling for 20 minutes lowers the amount to 59 international units (LEONG 1940a).

8 *Egg*—The results were based on the assumption that whole egg contains 60 per cent. of white and 30 per cent. of yolk. Vitamins B<sub>1</sub> and D are present only in the yolk and riboflavin in the white. The figure for aneurin represents the amount present in egg boiled for 10 minutes.

It is fully appreciated that the vitamin content of foodstuffs varies according to different observers, and that figures which are not worked out on the spot can only serve as a rough guide. (Since the compilation of the table fresh estimations for the composition of East African diets have arrived from the War Office.) It is also realised that the final amount is greatly affected by the method of cooking.

There has been some difference of opinion with regard to the protective level of thiamine intake but the figure in the table has been drawn from a report of the Technical Commission of the League of Nations 1938 which stated that an allowance of 10 international units per 100 calories seemed to be desirable. On the basis of this report it is considered that there was a deficiency in the diet of 124.6 international units for 2 months (when no meat was eaten) followed by a shortage of 59 international units during the ensuing 4 months. The beneficial effect of maize meal, beans and ground nuts, with their respective vitamin B<sub>1</sub> contents of 206, 159 and 410 international units per  $\frac{1}{4}$  lb can be appreciated by a study of the table.

In civil life Somalis should not usually be susceptible to beriberi in view of the fact that they consume milk (containing 272.6 i.u. thiamine per 4 pints cow's milk), especially camel's milk, and jouari or *Sorghum vulgare* (340 i.u. per lb) which is a form of millet. The town Somalis may also obtain eggs (65 i.u. per  $\frac{1}{4}$  lb) and bread (whole meal bread containing 500 to 600 i.u. per lb).

As the result of this outbreak of beriberi the Somali ration scale was altered and a new one drawn up. The high aneurin content of this diet is shown by a study of the constituents in the previous table.



## NEW DIET SCALE FOR SOMALI TROOPS

Commodity	Daily Scale	Commodity	Daily Scale
Jowari flour	16 oz	Orange	1
or Maize meal	16 oz.	or Sweet pepper (peprika)	$\frac{1}{2}$ oz
Rice	6 oz	or Ascorbic acid tablet	1
Fresh meat	8 oz.	Sugar	2 oz.
or preserved meat	6 oz.	or Jaggery	2 oz.
Ghee substitute	2 oz	Salt	$\frac{1}{2}$ oz.
Dates (pitted)	4 oz	Tea	$\frac{1}{2}$ oz
or fresh vegetable	4 oz	or Coffee	$\frac{1}{2}$ oz
Ground nuts	4 oz		
or Dried beans	4 oz		
or Dried peas	4 oz		

*Study of the Other Constituents of the Somalis Diet* with reference to the table

(1) *Calories*—According to theoretical calculations for Europeans at home it would appear that the Army ration supplies sufficient energy for moderate work, but, on the basis of an allowance of 2,400 calories for maintenance plus 225 and 300 calories per hour for hard and very hard work respectively a calorie intake of 3 686 only permits 6 hours of hard work or 4 hours of very hard work per day. It would therefore at first sight appear that, while sufficing for routine duties, the diet might prove hardly adequate for very active operations.

It is, however, important to realise that the African not only weighs less than the European, but also lives in a hotter climate. Moreover it has been shown that the average East African soldier does not consume the full ration supplied to him. It is therefore almost certain that the actual energy value of the Somali rations fully satisfies the requirements.

(2) *Protein*—Only the minimum requirement is present, but the addition of any one of the supplementary foods (especially beans which contain 26 grammes per  $\frac{1}{2}$  lb) would ensure a more ample supply.

There is probably no lack of protein in the normal diet of the civilian population.

(3) *Iron*—The diet contains the ample supply of 30 mg. of this metal.

(4) *Vitamin A*—There is considerable difference of opinion regarding the minimum vitamin A requirement. AYKROYD (1937) suggesting a minimum of 3 000 i.u. and ROSE, 1933 an intake of 140 i.u. per 100 calories. There can, however, be little doubt that the figure of 1 458 for the Somali troops is inadequate although there were no clinical signs of deficiency. None of the supplementary foods contains sufficient vitamin A to overcome the deficit, but the inclusion of ghee substitute, which contains a minimum of 3 000 international units of vitamin A per ounce, in the full ration scale makes good the deficit. Even the natural diet of civilian Somalis would appear only to provide enough

of this vitamin when a sufficient quantity of milk (containing 908 i.u. per 4 pints) and eggs (1 938 i.u. per  $\frac{1}{2}$  lb) is taken

(5) *Riboflavin*.—The riboflavin content of the diet has been included on account of the increasing interest in the clinical manifestations of ariboflavinosis. There was no evidence in these patients of cheilosis, keratitis, twilight blindness or cutaneous or tongue lesions such as have been ascribed to this condition, although a perusal of recent literature suggests that there was a dietary deficiency of approximately 2.4 mg. riboflavin. None of the supplementary foods would make good this shortage but a daily intake of 4 pints of milk in the civilian's diet would satisfy his requirement by supplying an extra 4.5 mg. of this substance.

(6) *Nicotinic Acid*.—The total for the Army diet is 16 mg. There was no clinical evidence of deficiency although the intake was similar to that found in the typical maize diet in Rumania (15 mg. per adult consumption unit) where the incidence of pellagra is high. It is interesting to note that, according to LEONG (1940b) the average daily diet of the Asiatics in Malaya probably contains no more than 10 mg. of nicotinic acid and that in India as shown by ATKROYD and SWAMINATHAN (1940) the typical rice diet contains 5 to 11 mg. per adult male consumption unit, whereas typical pellagra is rare in both these countries. As LEONG states these observations seem to indicate that the relationship between diet and pellagra cannot be explained in terms of the nicotinic acid content of the diet alone. Possibly other factors (as yet unrecognized) play a part in the causation of pellagra.

(7) *Vitamin C*.—The total of 13 mg. ascorbic acid falls short (by 17 mg.) of the 30 mg. required—some authorities consider that at least 50 mg. per day is needed (SINCLAIR, 1941). There was no evidence of scurvy but this is what would be expected in view of the long latent period of this disease which is usually about 8 months: the Somali troops had been living on their present diet for only 6 months. Moreover as stated in the footnote under the table of Somali diets (p. 58) the full ration scale allows for an ample supply of vitamin C and there was probably intermittent consumption of extra quantities of this vitamin when transport was available.

(8) *Vitamin D*.—The diet is deficient both in calcium, as is common in Africa, and in vitamin D. It is however well known that clinical signs of vitamin D deficiency are rare in all climates with a high annual incidence of sunshine.

It is interesting to learn that Capt. A. McDOWELL DAVIES, R.A.M.C. now encourages the Somali troops either to buy or to exchange their rations for milk from the nomadic people of the district. A study of the table will reveal that a daily intake of 4 pints of milk not only makes good the deficiencies of calcium, vitamin B<sub>1</sub>, riboflavin and vitamin C but also goes far to reduce the shortage of vitamin A.

It must be emphasized that the full ration scale contains ample quantities

of the various essential ingredients. Any deficiencies (which have now been rectified) were temporary and due to the inaccessible district in which the troops were operating and to the consequent difficulties of transport.

### SUMMARY

1 An account has been given of an epidemic of beriberi amongst Somali troops, who had been living on a diet containing approximately 244 international units of vitamin B<sub>1</sub> per day (with a deficit below minimum requirements of 124.6 I.U.) for 2 months, followed by 309 international units (with a deficit of 59 I.U.) for 4 months. There were altogether eighteen cases of the disease.

2 Neighbouring Somali troops, who had been taking the same rations for a period of only 2 months, showed no sign of the disease.

3 A table, giving the nutritive value of Somali diets, has been drawn up and demonstrates the high thiamine content of the supplementary rations prescribed, and the adequate amount of this vitamin in natural civilian foodstuffs.

4 The table reveals additional deficiencies of approximately 0.38 gramme calcium, 3,542 international units of vitamin A, 2.4 mg. riboflavin, 17 mg. ascorbic acid and 190 international units of vitamin D. The dietary shortage of vitamin D being compensated by the high degree of natural irradiation in East Africa, has probably little significance. These deficiencies were due to difficulties in supply and have now been corrected.

### REFERENCES

- AYERST W. R. (1938). *Indian Health Bulletin* No 23.  
*Field Service Hygiene Notes India* (1940) p. 337.  
 FIKEN, M. A. B. & ROSECOM, M. H. (1940). *Nutr. Abstr. Rev.* 9, 793-861.  
 LEONG, P. C. (1939). *J. Malaya Br. Brit. med. Ass.* 3, 219-223.  
 ——— (1940a). *Ibid.* 4, 66-107.  
 ——— (1940b). *Ibid.* 4, 261-278.  
*List of Food Values in Ration Scale of East Africa Command*  
 MOTTRAM, V. H. (1937). *Practitioner* 139, 71-72.  
 SHERELL, W. H. (Jr.), BUTLER, R. E., WOOLLEY, J. G. & IRELL, H. (1941). *Publ. Hlth Rep., Wash.* 56, 510-519.  
 SHERMAN, H. C. (1937). *Chemistry of Food Nutrition*, p. 568.  
 SUGGLAIR, H. M. (1941). *Practitioner* 146, 116.  
 TROWELL, H. C. (1943). *Lancet* 1, 43.  
 VIDLER & FELICIANO (1928). *Philipp J. Sci.*, 31, 351-357 quoted by LITCH, J. N. (1930). *Dietetics in Warm Climates*, p. 258.

## CORRESPONDENCE

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### GUIDANCE NOTES ON PERNICIOUS MALARIA

*To the Editor TRANSACTIONS of the Royal Society of Tropical Medicine and Hygiene*

SIR

The TRANSACTIONS Vol XXXVI No 2 1942 (which came last week) contains interesting discussions by distinguished malarialogists. One would not qualify the words of teachers of renown but perhaps one might pause awhile and stir a lazy pen for the possible interest of malaria minded Fellows.

Two hundred natives of a sleepy hollow long defamed in song and story as the haunt of fever demons awoke one day to find their home the victim of a modern boom. Planes took off where cattle roamed mule tracks changed to tarmac roads and night and day the roar of a nation's trade echoed through the hills and gorges and in a season the malarious valley a malarious valley still became the home of 30 000 non immunes—hobos of a dozen races. Amid these scenes one lived and worked and learned until one day the busy hum of traffic ceased and all was quiet once again. What we did and what we saw are past and gone but perhaps the local lessons learned are worth relating.

In a hundred per cent spleen rate valley the malignancy of whose fever had been noted even in the VIII century this mass of susceptible foreigners produced an annual fever rate of 250 per cent and gave us a clinical field of great interest. In a month it was clear that one's 10 years of experience in three continents was worth nothing.

One will not write of statistics and racial incidence nor debate on prevention and normal treatment nor yet describe any of the many instructive cases. It will be enough to give only the conclusions reached.

After three seasons one felt in a position to hold opinions and for the public good it was thought desirable to record these opinions to help new assistants

who came from time to time.—all men with years of malaria work behind them but with little knowledge of the type prevailing there in those days These guidance notes were —

### NOTES ON PERNICIOUS MALARIA IN

Pernicious malaria is an acute emergency in which even minutes may count. In no infection other than cholera is death so liable to follow the onset of symptoms so quickly

It is necessary therefore that pernicious malaria in its varied forms should be recognized at once To help to ensure this it is wise to think of malaria first last and always, even at the risk of missing other dangerous conditions

We have four main types of pernicious malaria here

A. *Algid* Patient collapses usually suddenly and is found cold, pulseless and often unconscious Treatment must be *immediate* Hot water bottles stimulant injections one pint of intravenous saline containing 6 grains of quinine bihydrochloride (if open operation is needed use a vein on front of ankle) Within 6 hours the prognosis is usually beyond doubt

B *Cerebral*. Two distinct varieties

1 Quiet Ranges from drowsiness (not to be confused with plague) to deep coma Usually fever of 103° or 104° F and often incontinence of urine and faeces Untreated such persons may live for a week Treatment is (a) Lumbar puncture (partly to relieve pressure which may be raised and partly to exclude meningococcal infection) (b) Intravenous quinine 6 grains in 10 c.c. water repeated 8-hourly until malaria drugs by mouth can be retained. Consciousness does not usually return in less than 18 hours

2 Rowdy Two types (a) Restless semi-conscious, noisy breathing, frothing at mouth. (b) Violent, presents various features of alcohol intoxication, ranging from a person who is just chatty to one who is fighting mad. These patients may be hard to catch and may need eight men to hold them down. Morphine is indicated and chloroform is commonly needed before treatment can be given They are liable to be dangerous they tend to wander about if not kept under morphia and they may attack people or come to a tragic end by jumping out of a window A guard is essential.

Both types should be nursed on the floor and not in bed Lumbar puncture and I V quinine are needed and removal of half a pint of blood may be desirable In the violent type treatment usually restores mental stability in 6 to 12 hours but in the restless type (which is often fatal) recovery is slower

C *Haemorrhagic* Main kinds are —

Epistaxis rectal bleeding petechial haemorrhages Generally only one of these features is present and often there is nothing else to suggest malaria. Treatment is I V quinine followed by anti-malaria drugs by mouth. We have had no success yet with vitamin K.

D *Gastro-intestinal* Four kinds

Persistent vomiting persistent hiccough intestinal colic choleraic (with collapse but rarely urinary suppression) Treatment is I V quinine until oral drugs can be retained In collapse call the shock squad. Morphine and chloroform are sometimes useful aids in hiccough cases

*Blackwater* Follow the usual lines Alkalinization and simple diuresis (glucose bicarbonate drinks a gallon a day) Quinine atabrin, methylene blue vitamin K, do neither good nor harm. Treat collapse with I V saline and as a general rule leave blood transfusion to convalescence

It is important to remember that the worst kinds of malaria have no resemblance whatever to the popular idea of the disease and that the term malarial fever is apt to be misleading The microscope has little place in the diagnosis of pernicious malaria. A negative blood slide has sent many to the grave

It is important to remember also that malaria may complicate co-exist with or be masked by any acute and many a chronic disease If the undetected malaria is of the pernicious kind the patient will die if it is of a less severe type it may so reduce the patient's resistance that he may succumb to the other condition. While you are here let not your diagnosis be \ disease make it \ plus malaria and you will not be mistaken often

Patients admitted with cerebral symptoms are the most confusing and it is in these that the superadded malaria is most likely to be missed Some of the signs of a case of cerebrospinal meningitis may be due to malaria We have a slide of C S F showing M T crescents side by side with meningococci

In head injury cases the signs of concussion may be due to or may be altered by malaria and may lead to a diagnosis of subdural haemorrhage if the C S F is bloodstained as it sometimes is in violent cerebral malaria. An unconscious driver removed from the wreckage of an upturned lorry may have crashed because he had cerebral malaria Such happenings are not rare here Do not repeat my mistake of forgetting malaria and doing an unnecessary trephine Every person brought in unconscious should be given I V quinine no matter what other treatment may be needed

Some doctors unaccustomed to I V quinine therapy are reluctant to use it as it is said to be dangerous In an experience of some 10 000 such injections one can recall no untoward effects though one's failure to use it promptly has led to many deaths

In cerebral cases when a lumbar puncture is done the quinine may be given intrathecally It saves time but it does not seem to have any therapeutic advantages

Quinine intramuscularly is absorbed more slowly than when given by mouth and in pernicious malaria it should not be used except for small children

A final tip Here where malaria is a killer a see what he s-like in the morning practice ends in disaster The prudent doctor decides quickly and then acts immediately One can do a lumbar puncture or give I V

quinine at the roadside by the headlights of a car and one should not fail to do so if the occasion arises.

These notes are to guide you until you know our malaria.

\* \* \* \* \*

A few other observations are recalled and may interest readers

1. Opium. Useful by mouth it is inferior to quinine. Morphine injections of doubtful value. We had no experience of treating malaria by opium-smoking only and data collected were insufficient to show if an average person who never had opium out of his system was protected. Labourers who spent their wages on opium-smoking rather than on food and were therefore greatly undernourished suffered much from malaria. Among moderate (pipe at bedtime) persons the incidence did not seem to differ from that of the general public.

2. Intramuscular quinine was in great demand by the public if abscesses had been common its popularity would have ceased. In our market-place some 2,000 such injections were given yearly but one heard of only one abscess.

3. After being got under control malaria may show an inversion of temperature thus a man who has had his fever at 5 p.m. daily may immediately after the fever is controlled show a decided drop below normal at 5 p.m. for the next 2 days.

4. The classical sweating stage of malaria may be due perhaps, more to the treatment than to the disease. During the shivering stage blankets are piled on and sweating follows the fever. In a series of personal experiments in several bouts of B.T. malaria in which treatment was withheld it seemed that (a) sweating happened only if blankets were used and (b) the immediate subsequent weakness was due to fluid loss and not to blood destruction. No blankets no sweating no weakness. So the busy man should avoid blankets.

\* \* \* \* \*

It is feared that this letter is very dogmatic. But it simply records the impressions of an observer working in a particularly malarious place. Its conclusions are not meant to have any wider application than to that place that community and that period.

I am, etc.,

D. KENNETH LINDSAY

Lt Col I.M.S.

# TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

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VOL. XXXVII No. 2. SEPTEMBER, 1943

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ANNUAL GENERAL MEETING  
of the Society held at  
Manson House, 28, Portland Place, London, W 1,  
on  
Thursday, 1st July, 1943, at 4 p m

THE PRESIDENT  
Sir S RICHARD CHRISTOPHERS C.I.E. F.R.S. Colonel I.M.S. (ret'd.)  
in the Chair

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## BUSINESS

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### REPORT OF THE COUNCIL FOR THE YEAR ENDED 31st MARCH 1943

The President presented the Annual Report, copies of which had been distributed beforehand

Sir Leonard Rogers proposed the adoption of the Report. This was seconded by Professor Blacklock and unanimously approved.

### REPORT OF THE HON. TREASURER FOR THE YEAR ENDED 31st MARCH 1943

The Hon. Treasurer, Dr OSWALD MARRIOTT presented his Report with the Accounts and Balance Sheet prepared by the Auditors Messrs. W B Keen & Co. and approved by the Audit Committee

Dr MARRIOTT called attention to the fact that this year the full amount of repayment of mortgage had been made as required by the Charity Commissioners

He also referred to the cheering news of a legacy of £5 000 (free of duty) from the late Mrs M K. COLDWELL, widow of Major COLDWELL. Dr MARRIOTT said there was reasonable hope that the amount of this legacy would be forthcoming before the end of the present financial year

The Treasurer's Report was unanimously approved and adopted.



## ELECTION OF AUDIT COMMITTEE.

Dr VINCENT HODSON, Dr W. E. COOKE and Col. F. P. MACKIE were re-elected as members of the Audit Committee.

RESULT OF BALLOT FOR PRESIDENT TWO VICE PRESIDENTS AND  
TWENTY COUNCILLORS FOR 1943-45

The PRESIDENT announced the names of those elected as follows —

*President*

\*Sir HAROLD SCOTT K.C.M.G., M.D., F.R.C.P., F.R.S.E.

*Vice-Presidents*

\*A. G. BIGGAM O.B.E., K.H.P., M.D. F.R.C.P., Major-Gen. A.M.S.

Sir HAROLD WHITTINGHAM, K.B.E., K.H.P., F.R.C.P. Air Marshal, R.A.F.

*Councillors*

\*A. R. D. ADAMS, M.D. CH.B. M.R.C.P., D.T.M.

D. B. BLACKLOCK, C.M.G. M.D., D.P.H. D.T.M. Professor

C. C. CHESTERMAN O.B.E., M.D. B.S., M.R.C.P., D.T.M. & H.

J. A. CRUICKSHANK, M.C., M.D., D.P.H., Major I.M.S. (ret.).

\*W. R. M. DREW O.B.E. M.B. B.S. M.R.C.P. D.T.M. & H., Lt.-Col. R.A.M.C.

✓ HAMILTON FAIRLEY C.B.E. M.D., D.Sc. F.R.C.P., F.R.S. Col. A.A.M.C.

R. M. GORDON O.B.E., M.D., M.R.C.P. D.P.H., D.T.M. Professor

E. D. W. GREIG, C.I.E. M.D., D.Sc. F.R.C.P.E., Lt.-Col. I.M.S. (ret.)

\*R. BRUNEL HAWES M.B., B.S. F.R.C.P.

\*W. H. KAUNTZ, C.M.G., M.B.E. M.D. CH.B. M.R.C.P.

GEORGE MACDONALD M.D., CH.B., D.P.H. D.T.M. Brigadier A.M.S.

Sir PHILIP MANSON BAHR, C.M.G. D.S.O. M.D. F.R.C.P., D.T.M. & H.

OSWALD MARRIOTT M.D., B.S. M.R.C.P.

F. MURGATROYD, M.D. F.R.C.P. D.T.M. Lt.-Col. R.A.M.C.

A. G. H. SMART C.M.G. M.B.E., M.D. D.P.H. D.T.M. & H.

HUGH H. SMITH M.D.

C. M. WENTON C.M.G. C.B.E., M.B. B.S. B.Sc. F.R.S.

F. NORMAN WHITE, C.I.E. M.D. Major I.M.S. (ret.)

VINCENT B. WIGGLESWORTH M.D. B.Ch., F.R.S.

CHARLES WILCOCKS, M.D. CH.B. D.T.M. & H.

*New Nominations*

The President (Sir Riehard Christophers) You have just heard the announcement that Sir HAROLD SCOTT has been elected our new President and in a few minutes it will be my pleasant function to induct him into his new office. In the meantime it is usual for the retiring President at this stage to make a few comments on the Society's history during his period of Presidency. Before I say anything further however I think you would wish me to say how deeply grieved all our members are to have heard of the death of Professor

WARRINGTON YORKE. We offer to his wife and family our deepest sympathy in their bereavement. Professor YORKE was one of our most active Fellows, a former Vice President, and one of the Society's Trustees. By his death we have lost one of our most outstanding research workers in tropical medicine. Professor YORKE's work covered a considerable field, but latterly was especially concerned with chemotherapy as related to tropical medicine in which he was, I think, without doubt the most outstanding figure in this country. His work has always been characterized by originality of conception and carried through with a lucid clarity which we could all copy with advantage. Many of us have lost a genial and delightful companion and many a very staunch friend.

I ought also to mention the names of three famous men, Honorary Fellows of our Society whose death has been reported during my term of office. They are Professor HANS ZIEMANN of Berlin, Professor BASILE DANILEWSKY of Kharkoff—a great name to all those who have worked in protozoology—and Professor C. W. STILES of the United States, a great authority on medico-biological taxonomy.

As regards the Society when war broke out and especially at the time of disasters in the Far East it looked as if our Society would suffer very severely in loss of membership and on that account and for other reasons we might possibly be in some financial difficulty. Certainly things did not look too good. However you have heard the report of the Council and the report of our Honorary Treasurer Dr. MARRIOTT and I may say with satisfaction that the affairs of the Society are by no means so gloomy as they then appeared likely to be. The number of Fellows has scarcely fallen at all, and financially we seem to be in a satisfactory position. We have also had, as you have heard, the very pleasant surprise of a legacy of £5,000.

Our meetings have not been so numerous as formerly. However there were a number of reasons for not holding them, the most important latterly being the considerable difficulty in getting suitable papers for meetings now that so many of our Fellows are abroad or if at home are so busy that it is too much to expect them to produce papers.

There is, however, one of the Society's activities to which I should like to make special reference, viz. our TRANSACTIONS. I do not think perhaps that Fellows always sufficiently appreciate the full advantages of that publication. It is not merely a record of our meetings; it is a first-class scientific medical journal to be found in all the libraries and second to none of the better journals. It has a very large circulation, because not only is it on sale as a journal but it is distributed to something like 1,600 of our Fellows all over the world. Its get up is attractive and it is very generous in its illustrative matter. Now my own experience has been that it is not always easy to get satisfactorily published a paper one may have written. Some may not have found this to be so but I think many authors do. In our TRANSACTIONS therefore, I think our Fellows have a considerable asset in the way of publication space. Any one of them sending in a paper may expect to be sympathetically treated to say the least.

I must not make my remarks too long, but conclude with a word of thanks to those Fellows who have done work for the Society. First of all however I should like to thank those members who whenever able to do so have turned up at our meetings, giving us very good attendances. The meetings being held in the afternoon, it must sometimes have been inconvenient to attend them. I thank also those who have read papers and taken part in the discussions. A word of thanks is certainly due from the Society to the Executive Committee who have done quite a lot of work during my term of office, what with the effect of the blizning and so on, and have met frequently. They are Dr CARMICHAEL, LOW, Dr WENTON and Dr MARRIOTT. Then, of course double duties have fallen on Dr WENTON as his Fellow Honorary Secretary. Col. HAMILTON FAIRLEY is as you know away abroad. I should also like to thank Miss WENTON and her office staff.

#### INDUCTION OF THE NEW PRESIDENT

It now only remains for me to perform the last rites of a retiring President and to induct the new President into his office. I do not need to speak about the claims of Sir HAROLD SCOTT to be our President, you know them as well as I do and I will ask him to come forward.

The President Elect, Sir HAROLD SCOTT came forward and the retiring President invested him with the badge and chain of office.

The President, Sir Harold Scott. Officers and Fellows of the Society. I am deeply sensible of this signal honour which you have accorded me in raising me by your suffrages to this exalted position. My gratitude is deep and sincere. Never in my wildest flights of fancy did I dream that I should ever come to sit in the chair which such famous men have occupied. I cannot hope to reach the lofty standard which they established, but one thing I can do and I think I can promise to do it, and that is during my term of office to strive to the utmost to maintain the prestige and honour of this great Society. My gratitude is all the greater because this will afford me opportunities of renewing again friendships which I feared were seyered for all time, when I retired from work in London last year. I will say no more except that once again I thank you with all my heart.

The first privilege of my new position is the nomination of a Vice-President, and I am glad to say that Dr H. M. HANSCHALL has consented to be my nominee. Dr HANSCHALL needs no introduction to the Fellows of this Society whose discussions he has adorned for so many years. As you are all aware, his knowledge of tropical medicine is both wide and deep and I must confess that in the times when I used to attend these meetings regularly one great inducement was the hope that I might hear him give one of his apt, apposite, witty, yes, and humorous contributions to the discussion. I feel sure the Society will benefit and be all the richer for his again returning to office.

(This concludes the business of the Annual General Meeting.)

## ORDINARY MEETING

of the Society held at

Manson House, 28, Portland Place, London, W 1,

on

Wednesday, 14th July, 1943, at 4.30 p.m

THE PRESIDENT SIR HAROLD SCOTT K.C.M.G. M.D. F.R.C.P.

in the Chair

## DISCUSSION

ON

### MODERN DRUGS IN THE PREVENTION AND TREATMENT OF TROPICAL DISEASES

Colonel S. P. James, in opening the discussion Professor WARRINGTON-YORKE's untimely death is still fresh in our minds. We were looking forward to hearing him deliver at the Royal Society to-morrow the Croonian lecture on Recent developments in chemotherapy with special reference to tropical diseases. I think you will agree that it would be a fitting tribute to his memory to base this discussion on some of the outstanding additions to knowledge which he made.

Let us begin with what he discovered about the treatment and prevention of malaria in 1924 and 1925. Dr MACFIE was working with him at that time so if he is here to-day I hope he will correct me if I do not do justice to their collaborative research.

Many of us will remember that in those years it was a common practice to treat malaria with very large doses of quinine and to continue to give large doses for a long time. The aim was said to be to sterilize the infection. Heroic efforts to that end were often made even as much as 190 grains of quinine being given daily for as long as the patient could stand these large doses.

YORKE was the first to examine scientifically by controlled experiments this practice of trying to sterilize a malarial infection by giving quinine in very large doses for a long period. He made three outstanding observations. The

first was that quinine, however and whenever it is given, does not prevent infection. The second was that at the onset of the primary attack, quinine has no action at all until a good many parasites are present in the peripheral blood. The third was that quinine, however and whenever it is given, does not prevent malaria from relapsing.

As everyone knows Professor YORKE based some new and at that time quite revolutionary recommendations for treatment and prevention on those observations but, in the time at our disposal I do not think it would be profitable to include them in our discussion to-day. They did not win the approval of clinicians and I doubt if they were ever acted upon in general medical practice.

But the theory put forward by YORKE and MACFIE to explain their observations was very interesting. It recalls the haemoclastic shock theory put forward by ARRAMI and SENEVET 6 years earlier. It is that quinine in whatever large dose it may be given, never destroys *all* the parasites in the peripheral blood. It destroys many but not all and those which it has destroyed act as an antigen which stimulates the host to produce an antibody or immune body which kills the remaining parasites. I think Professor YORKE attached more importance to this immune body as a killer of parasites than he did to the particular antimalarial drug that was used to start the mechanism by which the immune body was produced.

Unfortunately after 1925 Professor YORKE turned to other fields of research but his pioneer work was continued and extended at the Ministry of Health Malaria Therapy Centre at Horton Hospital, Epsom. Here his observations were repeated and confirmed and further knowledge was obtained particularly on the important part played by natural and acquired immunity in the curative process. The way in which malaria cures itself when it is not treated by drugs was studied and it was shown how quinine can be used to stimulate and to assist that natural curative mechanism instead of being used, as in the last war, in sledge-hammer attempts to sterilize the infection. In March 1931 these new ideas were presented at a meeting of this Society and in 1932—by which time the controlled experiments with quinine had been supplemented by experiments with plasmoquine and stebrin—were fully considered in the interesting Discussion on Synthetic Antimalarials and Quinine which you will remember was held in this hall in August of that year. Professors SCHULEMANN of Elberfeld, SWILLENGRABEL of Amsterdam, and CIUCA of Bucharest as well as Sir HENRY DALE, Dr T. A. HENRY and Sir DAVID PRAIN took part in that discussion at which the aims and objects of antimalarial chemoprophylaxis and chemotherapy were, for the first time, clearly stated. They were defined in terms of the selective action of quinine and the new synthetic drugs on the different species of the malaria parasites, the different phases of the same species, the different geographical strains of the various species, and the different races of mankind among whom malaria occurs. In 1933 and 1934 all the published results of controlled experiments made in laboratories, hospitals and in the field in various parts of the world were collected and examined by the Malaria

Commission of the League of Nations and recommendations for treatment and prevention based upon them were put out as the third and fourth general reports of the Commission under the title *The Therapeutics of Malaria*. These recommendations represented the considered opinion of some of the most experienced and distinguished malarialogists in the world including Professors NOCHT GIESSA MÜHLENS SCHÜFFNER SCHILLING MARCHOUX, BRUMPT ASCOLI MISSIROLI SWELLENGREBEL, CIUCA DE BUEN and PITTALUGA.

The recommendations were under five headings namely (1) True causal prophylaxis (2) Clinical prophylaxis, which is now called suppressive drug treatment (3) Treatment of the attack, a distinction being made between treatment of the primary attack and of an attack due to a relapse (4) Treatment to prevent relapses (5) Treatment to prevent spread (Gametocytetherapy)

This detailed and perhaps too logical classification did not make a strong appeal to the English mind but it was a scheme that gave great intellectual satisfaction to French members of the Commission who I believe regarded it as solving the whole malaria problem out of hand. All that was required in their view was to get chemists to discover the five necessary drugs or better still (as SCHULEMANN himself suggested at the Society's meeting in 1932) a polyvalent drug, effective for all five purposes.

Still whether those who will take part in this discussion have thought seriously about those recommendations or not I cannot help feeling that they should be the foundation on which to build.

Of course since those two reports were published a good deal more information has been obtained most of what is new having come I think, from research on avian malaria, particularly on *Plasmodium relictum* in the canary and on *Plasmodium gallinaceum* in the domestic fowl. Notable items of new knowledge acquired by these researches are a better understanding of the natural course of infections with malaria parasites of the manner in which the disease cures itself when left untreated of the mode of action of antimalarial drugs and most important of all the discovery of what is called the exo-erythrocytic cycle of the malaria parasite.

In the time allowed me for these opening remarks I can only touch on a few of those items so I shall select those which seem to have a bearing on the observations by Professor YORKE mentioned in the beginning of my talk.

What I wish to say will be easier to follow if I begin with a few words about the exo-erythrocytic cycle of the parasite. Doubtless all who are present know the theory which was put forward in 1931 that sporozoites injected by the mosquito have to undergo a preliminary cycle of development in tissue cells of the reticulo-endothelial system before they become capable of infecting red blood corpuscles. Also that during recent years schizogonic forms of this exo-erythrocytic cycle have been discovered so frequently in various species of avian malaria that it has become justifiable to assume that such a preliminary developmental cycle is an inevitable event in the life history of all species including those affecting human beings. In England the cycle has been studied

particularly in the avian parasites *P. relictum* of canaries and *P. gallinaceum* of domestic fowls. A few specimens of it are exhibited on the side table. This is not the first time that they have been shown at meetings of our Society but I daresay you will agree that they are worth seeing more than once.

Their origin, development and clinical and pathological effects can be observed with least difficulty in the domestic fowl. A good way in which to begin to study them is to inoculate sporozoites of the parasite *P. gallinaceum* on the chorio-allantoid membrane of chick embryos at about the tenth day of incubation of the eggs. After a drop of normal saline containing the sporozoites has been dropped on the membrane the window that has been made in the shell is closed with a coverglass and plasticine and the eggs are returned to the incubator for a few more days or until the chick hatches out or is about to do so. By making smear preparations from the brain, spleen and liver of one or more embryo chicks on different days after infection, one finds the asexual forms in cells of those organs and in leucocytic cells and monocytes in the blood. Rare, but quite unmistakable forms can be found in those tissue cells several days before any parasite can be found in red blood corpuscles. This proves of course that they are the first event in the life history of the sporozoites which were inoculated. The longer one continues incubation of the eggs after their inoculation, the more numerous the asexuals become until by the day on which the chick is due to hatch several forms are present in every field of the microscope. By that time too the red cells have become heavily infected with merozoites produced by the sporulation of the asexuals and the chick dies from the severity of the infection either before, or shortly after it has succeeded in emerging from the shell.

Evidently these very young chicks are much more susceptible to the parasite than older birds. This is also true in human malaria as is shown by comparing infections in new born babies with those in adults. The infection in chickens is always fatal to those under 2 weeks of age and it is fatal by the severity of the exo-erythrocytic infection rather than by that of the red cells. In fully grown and old birds the reverse is the case as it is often difficult in those birds to find any exo-erythrocytic parasites although one knows that they must have been present to start the red cell infection.

So if one were to set out to try to find these forms in human malaria the odds would be perhaps a thousand to one against success in any case except that of a baby heavily bitten by infected mosquitoes just after it was born. I mention this to counteract the conclusion which some observers have made that exo-erythrocytic schizogony does not occur in the human malaria parasites because they have failed to find it. Other observers have endeavoured to show that the exo-erythrocytic forms found in chickens were not developmental stages of the malaria parasite but were *Toxoplasma* or some other parasite.

With this preliminary explanation, let us assume that a sporozoite inoculated into a person by a mosquito is carried by the blood stream to a small capillary of the brain and that it pushes itself into one of the endothelial cells

which line the capillary wall. Being itself a tissue parasite it finds the cell a suitable home and begins to grow and to develop until by a complicated schizogonic process it produces an enormous number of tiny merozoites. They have a different appearance from that of merozoites produced by schizogony in a red blood cell and they have several other individual characters and peculiarities. As you can see in the slides under the microscopes they quickly enter the nearest red cells as many as eight or more being found in each red cell. One wonders how so many merozoites in the same red cell can all grow to maturity in so small a space. Another special peculiarity about them is that equally with the schizonts from which they arise they are quite unaffected by any known antimalarial drug. This has been found in repeated trials with quinine, atebria, plasmoquine, neostibosan (Bayer), undecane, 1, 11 diamidine dihydrochloride, 4, 4 diamidino stilbene, 4, 4 diamidino 1, 5 diphenoxy pentane and the sulphanilamide compound 'proseptazine'. Dr ANN BISHOP at the Molteno Institute, Cambridge, has found that when stel'in is given to canaries in maximum tolerated doses during and after the incubation period of sporozoite infections with *P. relictum* the first parasites which appear in the peripheral blood at the end of the incubation period are devoid of pigment and are quite resistant to the drug. Perhaps they are the special type produced by the first generation of exo-erythrocytic schizogony just mentioned. She has kindly put up a specimen of them for our inspection.

The therapeutic trials just mentioned together with comparable trials with quinine were made separately on birds infected by the bites of mosquitoes and on birds infected by the inoculation of malarial blood. It was found that in both prophylactic and curative trials the results obtained depend entirely on the presence or absence of exo-erythrocytic parasites in the treated birds. When the exo-erythrocytic type of parasitic multiplication occurs (as it does in all infections in the natural way by the bites of mosquitoes) none of those drugs when given daily in maximum tolerated doses throughout the period of the trial has any effect in prolonging the incubation period of the malarial attack or in preventing a fatal issue on or about the day on which untreated birds always die. But when exo-erythrocytic schizogony is absent (as happens often in infections by direct inoculation of peripheral blood) even a small dose of quinine or other antimalarial given on the day of infection followed by the same dose on the next day is always quite sufficient either to prevent the attack altogether or to delay its onset until the 20th day or later.

On the basis of this account we can now explain Professor FORKE's observations.

The first was that quinine does not prevent infection. As we know that exo-erythrocytic schizogony is the first event in mosquito infections and that these forms of the parasite are not amenable to quinine that is what we should expect.

The second observation was that quinine does not begin to act until a good



many parasites are present in the peripheral blood. Dr KORTEWEG of Amsterdam, made the same observation when he reported that quinine had no effect on the parasites which by thorough and prolonged search, he found during the incubation period of benign tertian malaria, and Professor SWELLENGREBEL made the same observation when he found that quinine has no action in the primary attack until the end of the period of "initial fever" defined by Dutch clinicians. The explanation, of course has just been given. Quinine has no action on the first brood of parasites in the peripheral blood because they are parasites of the exo-erythrocytic cycle.

The third observation was that quinine does not prevent malaria from relapsing. About this it does not seem necessary to say more than that quinine and other known antimalarials when used for clinical prophylaxis or suppressive drug treatment, will always fail when relapses are due to exo-erythrocytic forms of the parasite and will always succeed when the relapses are due to the ordinary endo-erythrocytic forms. This is obvious from the comparative experiments with direct blood inoculation and with sporozoite inoculation which I have mentioned. In cases of fowl malaria which recover from the primary attack and become chronic an interesting type of long relapse or recurrence often occurs about the 19th or 20th day after recovery. When a fowl dies from this relapse one always finds that the cause of death is a massive re appearance of exo-erythrocytic parasites in the internal organs and blood. I dare say it will already have occurred to you that this long relapse or recurrence on the 20th day in fowl malaria is comparable with the long relapse or recurrence of benign tertian human malaria about the 27th week. At any rate it is probable that the cause in both cases is the same for neither can be prevented by any plan of suppressive drug treatment yet discovered. For human benign tertian malaria this was proved in the experiment on medical students at St. Mary's Hospital which we made in 1931.

Lastly let me say a few words about YORRIS's suggestions for treatment. His idea was that by waiting until the peripheral blood contained many parasites and by killing most of them suddenly with a large "shock dose" of quinine one would start the natural mechanism of producing immune body which would complete the cure. On this view he recommended that treatment should be limited to three days during which six or seven grammes of quinine should be given. He found that the percentage of relapses after this short course was not higher than after prolonged treatment with the same or smaller doses.

The Horton practice of "aborting the attack" is based on the same principle which also receives support from the results of treatment of fowl malaria.

It was found by Professor BRUMPT in Paris and by ourselves in Cambridge that the best way to treat fowl malaria is to give a single large dose of atebuin at a time when many parasites are in the peripheral blood. Further dosage on subsequent days makes no difference to the speed with which parasites are reduced or eliminated indeed it may be harmful by interfering with phagocytosis.

That is one of the reasons why there is a good deal to be said for the practice in human malaria of initiating treatment with at least one large 'shock producing' dose

After I had written this I came across a paper on Heavy atebirin dosage in the treatment of malaria by Major J BRYANT which was published in the *East African Medical Journal* for January 1942 I agree entirely with what is recommended in this paper except to wonder whether the after treatment with quinine and plasmoquine is really necessary

Incidentally I was much struck, too by Major BRYANT's postscript to his paper I will not repeat it here as I hope that everyone will read the paper for himself Perhaps however Dr NICOL, from the point of view of a psychiatrist will say a few words on the neuroses following prolonged quinine treatment.

One sees then that according to these findings and explanations causal prophylaxis, clinical prophylaxis and suppressive drug treatment are bound to meet with only a very partial success until a new drug is found that will destroy parasites of the exo-erythrocytic cycle Of course that does not mean that the practice of suppressive drug treatment should be discontinued until that discovery is made It means only that the practice should be used intelligently with knowledge of its limitations Obviously nothing is gained by using large doses for suppressive treatment. We know that the onset of the relapses cannot be prevented by even the largest doses but we know too that if we take a moderate or even a very small dose daily the relapses will not last longer than 1 or 2 days because by the end of that time the exo-erythrocytic parasites will have completed their first cycle and the red cells will now contain only the type of endo-erythrocytic parasite which is very susceptible to quinine

I am afraid you may think I am making heavy weather of this antimalarial problem and that my account of it has been tedious but I cannot help feeling that a primary purpose of our discussion should be to try to explain to chemists who are working hard to find new antimalarial drugs precisely what our difficulties are and what it is that we require Some of you may remember that Sir DAVID PRAIN at the discussion on synthetic antimalarials and quinine which I have already mentioned in praising chemists for their courage resource and perseverance said that what they had already accomplished justified the belief that when medicine is in a position to tell chemistry exactly what medicine requires the chemist will in due course deliver the goods

Anyhow the desirability and the urgency of organizing a special research in England to find a drug that would destroy malaria parasites of the exo-erythrocytic cycle was put to the appropriate authorities more than 6 years ago I haven't heard that as yet anything extraordinary has been done about it

I must apologise for having spoken at such length in opening this discussion and for having limited my remarks to malaria but at the present time discussion of this disease must certainly take first place For in the light of past experience we all know that our very limited knowledge of how best to prevent and to

untreated controls. In *Brucella* infections (Malta fever and abortus fever) helminthiasis, protozoal infections excluding malaria, rickettsial infections (typhus, Rocky Mountain fever etc.), spirochaetal infections, tularaemia, typhoid and virus diseases—sulphonamides are useless, and to a certain extent harmful. None of these diseases should be treated by sulphonamides.

### *Sulphonamides and malaria.*

These compounds have some effect on malaria, but this effect is more of theoretical interest than of practical importance. As the pages of the *Tropical Diseases Bulletin* show there have been many papers on this subject both experimental and clinical, during recent years. As a result of all this work, to which WARRINGTON LORKE contributed, it appears that the newer sulphonamide compounds, like sulphathiazole and sulphadiazine, have quite a powerful effect upon human malaria, an effect which is greater on the malignant subtertian than on the benign tertian form. A large dosage is required, however, and the response is less certain than that to quinine or atebryn. If quinine or atebryn were not known, sulphonamides would be extremely valuable for the treatment of malaria. As these more powerful drugs are available, the antimalarial action of sulphonamides is of interest chiefly because it may form the starting point of chemotherapeutic research which may eventually yield more active compounds.

### *Blood concentrations*

Experience with sulphonamide chemotherapy during the last 8 years has made us familiar with two principles which might be advantageously adopted with some other drugs also. These principles are

Firstly control of dosage by estimation of blood concentrations, and secondly the starting of treatment by a big initial "loading" dose. The response of an infection to a drug depends on how much of the drug there is in the tissues, not on how much has been poured down the patient's throat. Although the same dosage may be given to a group of patients, some of them will have a much lower concentration of the drug in their blood than others do, and so a smaller chance of being cured unless this defect is remedied by increasing the dose. This consideration is less important as regards drugs which have a powerful short lived action, like the organical arsenicals for syphilis or sleeping sickness, but it is very important for drugs which exert a moderate but persistent action over a longer period, such as sulphonamides themselves, or as suramin (Bayer 205 antrypol) for the treatment of sleeping sickness. A method was devised by Professor WORMALL in 1937 for the estimation of Bayer 205 in the blood, which is much like the test that MARSHALL later introduced for sulphonamides, and I used this method to examine the blood concentration in a large number of patients with sleeping sickness. Although a standard course of treatment may have been given, in about one case out of twenty the blood may contain hardly any of the active compound.

Such patients give a temporary clinical response, which may be quite deceptive, and then a few weeks later, when perhaps they are no longer under medical supervision they relapse again. And a relapse in sleeping sickness particularly in the East African form is a very serious matter which may involve the disease establishing itself in the central nervous system and all chance of complete cure being lost. In the present state of medical services it is not possible for sleeping sickness teams in the bush to carry out such tests but I would strongly urge that in the case of all Europeans treated for sleeping sickness an estimation of the blood concentration should be made after the first week or fortnight, and that future dosage should be regulated accordingly.

### *Principle of the loading dose*

The second principle derived from experience with sulphonamides is the principle of starting treatment with a large initial or loading dose. In a case, treated by the usual principle of equal doses, the blood concentration rises gradually with each dose until eventually after the lapse of a longer or shorter period, it reaches the level necessary for therapeutic action. All this interval of time has been wasted and there has been an unnecessary delay before effective treatment really began. If a large initial dose is given, the effective level in the blood is reached almost at once and then it is maintained by smaller doses given at convenient intervals. The circumstances in which I suggest this method might well be adopted are firstly sleeping sickness treated by Bayer 205. In this case, the first two or three doses might be given in quick succession so as to build up the blood concentration quickly. Secondly malaria treated with atebirin. I have not sufficient clinical experience to name exact doses for atebirin but I would suggest that instead of giving the customary 0.1 gramme three times a day (in which case effective treatment probably does not begin until the second day), the first dose might be much larger e.g., 0.6 gramme and that this should be followed by 0.1 gramme given three times a day or possibly twice a day according to experience. Major BRYANT, to whom Colonel JAMES has referred advocates 0.9 gramme for the first dose.

If the patient can take atebirin by mouth, this is obviously the best route and it should always be used by preference. If he cannot take it by mouth, because he is vomiting or comatose or some other reason, then it will have to be injected and two routes are possible intramuscular or intravenous. Animal and clinical experiments have shown that atebirin reaches the blood rapidly after intramuscular injection. On the other hand, some histological studies which I made recently showed that it always caused a definite amount of necrosis at the site of injection, although less than quinine causes. Consequently it seems that the choice between these two routes lies between the certainty of a limited local necrosis if atebirin is injected intramuscularly and the remote but unpleasant risk of sudden death if it is given intravenously. The slower the intravenous injection, the smaller will be the risk. The choice

must be left to the experience and discretion of the medical man in charge of the actual case.

Dr H M Hanshell Mr President, may I say a few words of comment on papers that I have listened to with interest and profit. I think perhaps Colonel JAMES is impatient with the chemists. I am sure that if we clinicians tell them precisely what we want they will nowadays deliver the goods. But the first thing lies in that word precisely and it is hardly enough to say there is a special form of parasite which needs a special drug we must tell the chemist very much more about the bionomics of the parasite.

Dr HAWKING has said that there is likely to be an extended trial of propamidine other than for trypanosome infection. I am recently indebted to Messrs. May and Baker for a supply of propamidine. I find it has a curative effect, given intravenously on chancroid ulcers, but in the three cases so treated, cure was not more rapid than with sulphanilamide, or sulphathiazole, by mouth. moreover intravenous propamidine produces a fall of blood pressure with flushing of skin which may be alarming to the operator. Given intravenously on 3 consecutive days to one case and on 5 consecutive days to another case of lymphogranuloma inguinale, definite reduction in mass of inguinal gland tumours followed and a rapid disappearance of the redness of the skin over tumours. Much the same results sometimes follow the mere rest in bed which these patients enjoyed. In these five male patients, each about 150 lb bodyweight, the dose given intravenously was 20 centigrammes. In two cases of *Trichomonas vaginalis* infection, insufflation daily of the propamidine powder into the vagina after dettol cleansing and saline wash tried for 3 consecutive days was followed by rapid diminution of both labial redness and inflammation and purulent discharge and disappearance, at any rate for the time being, of the trichomonas from wet preparations of vaginal exudate. No recurrence of symptoms 4 weeks later. I support Dr HAWKING in his warning against intramuscular injections.

Major J W Howie May I offer a few remarks on the results of serial Tanret tests which seem to have some bearing on the administration and dosage of quinine in malaria? I venture to offer them since, as Dr HAWKING has said one of our needs is to devise and apply methods of estimating the various drugs, in the blood, which we use in tropical medicine. Major R M MURRAY LYON and I, although unable to use any of the rather difficult methods of estimating quinine in the blood, sought to control dosage by examining for quinine in the urine not in one specimen only as is often done to test absorption, but in every specimen passed by the patient under treatment. We applied this procedure to 100 British soldiers in hospital suffering from sub-tertian malaria in Southern Nigeria. We examined all urines from these 100 men, first during treatment while they were having 30 grains of quinine by mouth daily in doses

of 10 grains three times a day in liquid form and again during convalescence when they were having the usual suppressive dose of 5 grains daily. We took precautions to ensure that the dose was not evaded and as controls, we examined in the same way all urines of fifty three fit men in the same area who had taken the daily dose of 5 grains. Our Tanret reagent gave a positive reaction when quinine was present in any concentration greater than 1 in 200 000. Let us consider the normals first. All these fifty three fit men on 5 grains of quinine showed positive Tanret reactions in one or more specimens of urine but positive results did not appear within 15 minutes nor did they persist for 24 hours as they are often supposed to do. Only twenty of these fifty-three positive reactions appeared within the first hour and many had again become negative within 12 hours. One wonders about the French soldiers in Salonika during the last war who were punished for having evaded their quinine if the urine examined at any time after a 6-grain dose showed a negative Tanret reaction.

Our investigation of the 100 men under treatment for acute attacks with 30 grains of quinine daily in liquid form by mouth, showed that eighty-eight of the 100 men gave positive Tanret reactions in every specimen of urine passed and rapidly became well. Of the remaining twelve men, there were seven whose reactions were negative in every specimen of urine. These seven men were all acutely ill. Six were given intravenous quinine they recovered rapidly and at the same time their Tanret reactions not only became positive but remained positive on the doses of quinine by mouth which had previously been insufficient to give such a result. Five of the twelve were positive only at irregular intervals they were not acutely ill but their recovery was slow and their temperatures did not become normal for 5 to 7 days. We did not give them parenteral quinine although, in the light of our findings we now believe that it was indicated. Only one of these twelve men was vomiting and it may be that their failure to show quinine in the urine was in part due to errors of metabolism and excretion and is not to be explained solely as a failure of absorption. We examined the same 100 men during convalescence when they were taking the daily suppressive dose of 5 grains of quinine and found that eighteen of them failed to show a positive reaction in any sample of urine passed during the 24 hours following that dose. Six of these eighteen had also been negative during the acute attack. We went into the histories of the six men and found that all had suffered repeated attacks of malaria at short intervals in spite of taking 5 grains of quinine daily. We felt that this was significant when considered in relation to our finding that on this dose they were never able to excrete free quinine in the urine in amounts sufficient to give a positive Tanret reaction. It would of course, be desirable to do quinine estimations in the blood as one does with sulphonamides but our resources did not run to that. It seems to us, however that our procedure of controlling therapeutic dosage in the individual by ensuring that enough of the drug is given to maintain a steady output in the urine is not only easily carried out but is a good second best to estimations of quinine in the blood.

people taking the drug whereas in other groups there is little or no trouble only about 1 per cent. complaining of gastro-intestinal symptoms. No reasonable explanation of this variation in reaction can as yet be offered. However high the incidence of symptoms in the initial period, tolerance is acquired in 10 to 14 days, symptoms then ceasing in the great majority of those on suppressive mepacrine. Careful observations are being made on personnel on the larger doses of suppressive mepacrine over prolonged periods to determine the effect of this administration.

Regarding the statement by Dr NICOL that soldiers are being admitted to hospitals in this country suffering from overdose with quinine, all I can say is that our instructions are that men returning from certain malarial areas overseas shall continue suppressive mepacrine for stated periods and that quinine shall not be used for this purpose.

### *Bacillary Dysentery*

There is little to add to the work already published on the excellent results of sulphaguanidine in the treatment of this disease. Other preparations of the sulpha group have been found to give good results in the treatment of bacillary dysentery but sulphaguanidine is safer than most owing to the absence of toxic reactions and the rarity of ill effects on the kidney. Trials with succinyl sulphathiazole (sulphasuxidine) are being carried out and the results so far are most encouraging the smaller effective dosage of this drug is an advantage.

### *Diamidinostilbene (stilbamidine) in the treatment of kala-azar*

Recent reports suggest that even with freshly prepared solutions of this drug toxic effects, especially on certain of the cranial nerves, may occur after treatment has been completed. This drug which has been of great value in resistant cases of kala azar should therefore, I consider be reserved for use in the treatment of such resistant cases.

Dr A R D Adams I had not intended to speak, and so am rather unprepared. Nevertheless, as the sole representative of the Liverpool School here today I feel I ought to say something when so much reference has been made to Professor YORKE's work. I have been closely associated with Professor YORKE for a good many years, and I feel that he would not have agreed with a certain number of the statements made this evening. He was essentially a realist, and with reference to the exo-erythrocytic cycle of the human malaria parasite, I am not satisfied that he was entirely convinced either that such a stage existed or that this cycle accounted for most of the difficulties in the radical treatment of malaria. He was open to conviction, but I think he would have preferred to have seen these forms of the parasite himself rather than to have accepted their presence merely on analogy. I feel certain he would not

have blamed the chemists for failing to produce a drug to destroy these forms until he had at least demonstrated them to the chemists. As to the treatment of malaria, we in Liverpool, in contradistinction to some workers would seem to have been extraordinarily fortunate in our use of quinine. We treat a great many cases there—last year we had about a thousand—chiefly from West Africa. These with few exceptions were cases of malignant tertian malaria. We find that 30 grains of quinine a day given for 3 consecutive days by the oral route, are invariably effective in arresting the clinical attack. We very rarely indeed give quinine by the parenteral route. Lately we have been using mepacrine to forestall relapses. I have no doubt that YORKE would still have recommended the use of quinine for the acute attack because of the rapidity and certainty in action of this drug. He was not entirely satisfied that mepacrine was a safe drug as he undoubtedly considered quinine was but under the present conditions of quinine supply he was content to discharge seamen, after treating an acute attack of fever with quinine with a supply of mepacrine for suppressive and prophylactic treatment, even when these men were sailing in ships carrying no surgeons.

In regard to the diamidines we in Liverpool have treated some cases of kala azar with them and have been fortunate in avoiding the graver toxic manifestations described this evening. We have not treated a great many cases and we have been conservative in our dosage. Admittedly these cases have been Indian forms of the disease, and not the Mediterranean or Sudanese. I have seen a number of reports from the Sudan but I did not realise there had been many examples of the grosser toxic manifestations mentioned today. I understood that the toxic effects occurred chiefly where solutions of stilbamidine had been made up in bulk and therefore where the dose had been given some time after the drug had been put in solution. I have not the latest information on the point, so I cannot personally say how often these more serious manifestations do occur. Nevertheless the risk of toxic effects would appear to be justified in cases of the otherwise fatal Mediterranean disease, and it does not constitute a contra indication to the employment of the diamidine drugs.

Colonel S. P. James, in reply said he regretted that his opening paper had given the impression that he felt gloomy and pessimistic about the future of chemotherapy in this country. He was sorry too that Dr HANSCHELL had gathered that he was impatient with the chemists. The purpose of what he had said was simply to draw attention once again to the urgent need of creating in England a chemotherapeutic research and drug testing organization on an adequate scale in which chemists and biologists would work together in close association and with a common aim. This was an object for which Professor YORKE and others had striven unsuccessfully for many years. Everyone knows of course that, in England, arrangements for chemotherapeutic research and for the discovery and testing of new synthetic drugs have always been



inadequate and unsatisfactory and everyone hopes that sooner or later some thing will be done about it. But this desirable end will not be brought nearer by continuing to report that we are as content with quinine and atabrin as some speakers seemed to be. To adopt that attitude is tantamount to giving the administrative authorities who are responsible for organizing chemotherapeutic research yet another excuse for continuing to bury their heads in the sand. Major HOWIE's contribution to the discussion provided a further argument for the creation of a special organization in which fundamental chemotherapeutic problems would be studied including of course, the physiological chemistry of the absorption, metabolism and elimination of quinine and atabrin and their mode of action on the parasite. Twenty or more years ago it was thought that the only useful portion of a dose of quinine was the portion which escaped destruction in the liver and other organs and was eliminated in an unchanged condition in the urine. I have not looked up the literature to ascertain whether any further knowledge on the subject has been obtained since that time.

Major General BIGGAM and Dr. HAWKING mentioned recent work in the United States relating to the quantitative estimation of atabrin in the blood. Professor E. C. DOONE, of the Courtauld Institute of Biochemistry has begun an investigation of this subject and I hoped he might have been here this afternoon to tell us about it. Unfortunately he was unable to come, and all I can say on the matter is that it seems as if the research may be somewhat more complex than would appear from the scanty literature available. One practical difficulty is the necessity of withdrawing at least 20 c.c. of blood for each estimation.

Dr. NICOL's description of the experiment in true causal prophylaxis which he and Mr. SHUTE conducted was of great interest. He said, very truly that if the same experiment were made on a large scale in conditions similar to those of malarious war regions, a quick answer would be given to two questions that are frequently asked. Proposals for arranging a series of experiments of this kind on a large scale were made to the appropriate authorities some time ago. The success of the experiment at Horton was attributed to the destruction of the sporozoites by the atabrin shortly after their injection by the mosquito. Now that it has become possible to estimate the amount of atabrin in the blood it should not be difficult to ascertain by experiments *in vivo* whether that interpretation is correct or not. The method of conducting such experiments was described in 1927\*.

\* JAMES, S. P. NICOL, W. D. & SHUTE, P. G. (1927) Note on a new procedure for malaria research. *Trans. R. Soc. trop. Med. Hyg.* 21 (3), 233.

## COMMUNICATIONS

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### A CASE OF LEPTOSPIROSIS IN SOUTHERN NIGERIA

BY

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AND

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Jaundice is a fairly common condition in Nigeria, as is indicated in the Annual Medical Reports. Those for the years 1936 to 1938 inclusive (NIGERIA, 1938, 1939-1940) indicate that, in all, 2,162 cases were treated at the various Government hospitals during that period, an annual incidence of 0.036 cases per 1,000 of the total population, or 1.09 cases per 1,000 hospital patients. Whilst it may be assumed that a proportion of cases do not apply for medical treatment, the number so missed is probably not very large for by now there are few areas which have not experienced outbreaks of yellow fever and the more educated among the indigenous population are not only aware of the importance and dangerous nature of this disease but are prone to think that it is present and report accordingly to the nearest Medical Officer whenever they experience an attack of malaria accompanied by the passage of dark coloured urine, even though no jaundice is present.

Of the 2,162 cases of jaundice referred to above 152 were entered as cholecystitis, only forty as yellow fever and the remaining 1,970 as catarrhal jaundice. It will be appreciated that only a very small proportion of the jaundice cases reported came from centres where any immediate or complete laboratory investigation was possible so that any one of them may in fact have been one of several different diseases.

Leptospirosis has been reported several times in Central and West Africa. KADANER and CORTI (1933) investigated an epidemic of fever with jaundice in Stanleyville. Of the sixteen cases (all Europeans) three sera were sent to PETTIT in Paris who found them to agglutinate *Leptospira ictero-haemorrhagiae*.

\* We wish to express our thanks to Dr J. W. P. HARKNESS, Director of Medical Services, Nigeria, for permission to publish this paper.

to a high titre and two of these sera were further confirmed by SCHUFFNER in Amsterdam. SCHWEITZ (1933) also concluded that leptospirosis occurred in Stanleyville. During an epidemic among the native population one serum was found by both PETTIT and SCHUFFNER to agglutinate *L. ictero-haemorrhagiae* to a titre of 1/10 000. In examining 125 sera from French West Africa, GOEZ (1933) found that seven agglutinated *L. ictero-haemorrhagiae* (Verdun strain) to a titre of 1/1 000 but VAN RIEL (1942) criticises these results with the remark that a titre of 1/1 000 is only of indicative value. GRAY (1936) encountered a clinically typical case of leptospirosis in a European who bathed in a swimming pool in the Cameroons. Leptospirae found in the centrifuged urinary deposit proved typically infective to guinea-pigs, and the serum tested in Hamburg agglutinated classical *L. ictero-haemorrhagiae* to a titre of 1/300. KOLOCHINE ERBER and STEFANOPOULOU (1939), in the examination of 124 sera from French Equatorial Africa found that sixteen out of ninety three sera from Brazzaville gave feebly positive reactions against *L. ictero-haemorrhagiae* (Verdun strain) and that of twenty-one sera from various other districts, six agglutinated three European strains. These authors concluded that leptospirosis is more common in French Equatorial Africa than is generally believed, and that it is desirable to test such sera against a number of local strains of leptospira. Finally VAN DEN BERGHE and VAN RIEL (1939) isolated a strain of *L. ictero-haemorrhagiae* during an epidemic of pyrexial jaundice in Kivu Belgian Congo. Cross agglutination tests with the classical strain and with *L. canicola* showed that this was a distinct serological strain, but the authors considered it unwise to give it a new specific name.

Leptospirosis has also been reported from the Canary Isles by MARTIN SANCHEZ (1936) and this being a normal port of call for West African shipping it can be assumed that there was a considerable interchange of rat population in the days before the enforcement of anti rat precautions.

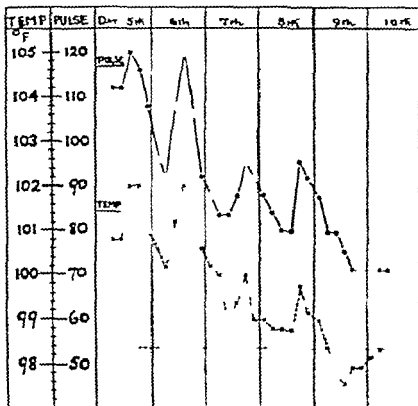
In view of these various reports from adjacent territories it was natural to suspect that some of the Nigerian cases of jaundice were due to leptospiral infection. Indeed thirty three cases were so reported in the *Annual Medical Report for 1930* (NIGERIA, 1932) but none of these was admitted to hospital so that it is doubtful whether the diagnosis had any but a clinical basis and since that date no further case has been recorded as being of leptospiral origin.

The present case was seen at Oshogbo Oyo Province Southern Nigeria but the man evidently acquired his infection in or near Ibe, in the same Province but about 30 miles distant.

#### CASE HISTORY

The patient, M. A. an African male aged about 26 years, was a literate well-spoken and intelligent young man. On 2.10.42 he boarded the bus to return from Ibe to Oshogbo, when, about 6 miles out on the road, he was suddenly attacked by severe fever. He continued his journey reaching home the same day. By this time he was experiencing severe backache and frontal headache. The pain prevented him from sleeping and he felt continuously thirsty. On 3.10.42 (4th day of the disease) there was epistaxis and a black stool was passed and on the same day someone told him that he was jaundiced.

He was seen and admitted to hospital on 6/10/42 (5th day) when his sclerae showed marked congestion and icterus and he was obviously extremely weak and ill. The temperature was 100.8° F., and the pulse 112 per minute. The tongue was red at the tip and sides and coated on the dorsum. The palate was congested. The liver and spleen were not palpable but the generalized slight abdominal tenderness was much more marked under both costal margins. The urine showed a large quantity of albumin and a heavy deposit of hyaline and granular casts. Bile was present in large quantities. A thick blood-film stained with Field's double stain showed no malarial parasites, trypanosomes, nor spirochaetes. Thereafter the temperature swung between 99.0° F. and 102.4° F., gradually settling to normal 3 days later (Fig. 1). The patient remained constipated for 3 days after which a saline purge resulted in the passage of normal stools. No vomiting or bleeding from the gums occurred at any stage of the disease. On 10/10/42 (9th day) the patient was afebrile, albuminuria was reduced to a trace and both bile and casts were entirely absent from the urine. He was discharged in perfect health 11 days later.



#### LABORATORY FINDINGS

Serum taken on the day of admission (5th day of illness) and submitted to the mouse protection test for yellow fever was found to be negative. The remainder of the serum was tested for the presence of agglutinins to *L. ictero-haemorrhagiae* using a 7-day live culture of *L. ictero-haemorrhagiae* (Wijnberg strain). This was supplied by Dr J. W. Howie, formerly of the Bacteriology Department, Aberdeen where this strain (originally obtained from SCHÜFFNER in Amsterdam) has been successfully used for some years. The technique employed was that of SCHÜFFNER and MOCHTAR (1927) as described by DAVIDSON *et al.* (1934). The result was negative. A second specimen of

serum taken on 21.10.42 (20th day of illness), was examined, when the mouse protection test was again negative, but the leptospiral agglutination test was positive to a titre of 1/1 000. This was confirmed by Dr Howe, using his own leptospiral culture and control serum. Serum taken on 9.11.42 (39th day of illness) showed a drop in titre to 1/300 thus indicating a recent leptospiral infection. A portion of this specimen was sent for retesting to Dr J SMITH City Hospital, Aberdeen who likewise reported that it agglutinated his leptospiral strain to a titre of 1/300.

#### DISCUSSION

In investigating a case of jaundice in West Africa the exclusion of yellow fever is naturally the first consideration. Ife was the scene of an extensive epidemic of that disease in 1928 (BEEUWKE, 1936). Two groups of children then showed respectively 68 per cent and 72 per cent. of positive mouse protection tests but many non-immunes must have arrived and settled in the town since then so that the present case could have been part of a new epidemic of yellow fever. The reported *Aedes* index in Ife was 5 per cent and this must be taken as a considerable understatement since ordinarily when the African Sanitary Inspector does his rounds, the news of his coming precedes him and results in the hurried emptying of many pots that are probably breeding places. Ife has a population of approximately 30 000 but as at the time of the 1928 epidemic, there is no doctor resident there and a good many deaths, or considerable absence of scholars from school, would have to occur before any epidemic was noticed. The present case could, of course, equally have been one of yellow fever of sylvatic origin.

At the time of admission the patient's pulse was 120 with a temperature of 100.4° F. Whilst this seemed to indicate the absence of Faget's sign BEEUWKE's careful analysis indicates that in Africans at least this sign is absent in approximately one-third of all cases of yellow fever. Comparison of this man's other symptoms with those of BEEUWKE's series likewise failed to reveal any special point which would exclude yellow fever.

Nevertheless, the patient's further progress in hospital made that disease increasingly unlikely. Pyrexia lasting as long as 8 days is in itself unusual in yellow fever and the close parallelism of pulse and temperature throughout would be very unlikely to occur in a case of such duration.

Relapsing fever seemed to be excluded clinically by the termination of the pyrexia by lysis rather than by the crisis characteristic of that disease and by the absence of spirochaetes in the blood film though less weight could be given to this, since in relapsing fever they tend to disappear from the blood 24 to 48 hours before the crisis. The form of the temperature chart was quite unlike that seen in early syphilitic hepatitis, or in liver abscess (in which jaundice is in any case of rare occurrence). The absence of vomiting and of parasites in the blood served to exclude the bilious remittent type of malaria.

Leptospirosis was not at the time very seriously considered for a rather similar case seen at Oshogbo early in 1941 had been reported as negative when the serum was tested in London. It is unfortunate that the only detailed investigation of the present case in hospital was performed on the 5th day of the disease since leptospirae have usually disappeared from the blood by then whilst they have hardly begun to appear in the urine. The examinations carried out on that day therefore failed to exclude leptospirosis but could scarcely be expected to confirm it. The results of the later agglutination tests, however appear to leave no doubt that this was a case of leptospirosis.

The mode of infection remains uncertain. The patient was a mechanic by trade, so that any occupational risk could be excluded. For about 3 weeks before the onset of the present illness he had been at Ife where he stayed with the African Pastor of the C M S Church. The house was a cement-faced one storied building with a corrugated iron roof but the lower part of the cement was somewhat dilapidated, and what was possibly a rat run was observed at one point. The inhabitants had noticed no particular prevalence of rats. Water used in the house was drawn from a public tap nearby this supplying untreated water from a reservoir outside the town. The only occasion on which the patient came in contact with any other water was about 9 days before the onset of symptoms, when he visited a farm about 13 miles outside Ife, and bathed in a small river about 50 feet in width, shallow and swift flowing but heavily shaded in parts.

There was no illness in the Pastor's family whilst the patient was at Ife, and examination on 7.10.42 showed that everyone was still in good health. The house was revisited on 12.11.42 and again no illness was found. The patient's food at Ife was the same as that of the Pastor's family and the eating of any thing contaminated with rats urine appears unlikely in view of the type of person affected and the kind of people with whom he was lodging.

JORGE (1931) is quoted by STRONG (1942) as describing an epidemic in Lisbon in which a leptospira was isolated from a public fountain but it is not mentioned whether this had a piped supply or whether it was open to direct inoculation by rats. *L. ictero-haemorrhagiae* has been shown to survive in moist soil for as long as 3 months but leptospirosis has not generally been regarded as a disease associated with defective water supplies and although the water at Ife is not chemically purified or filtered, the reservoir is nowhere of any great depth, and a considerable degree of sterilization must occur through the action of the sun's rays. The reservoir is situated in the hills some miles outside the town and holds about 4 days supply. A strip 100 yards wide round the margin is cleared and under short grass and conditions generally are not such as to be attractive to rats, whose holes are in fact, but few in number.

The patient at no time took part in any farming or other occupation likely to bring him into contact with infected mud and there remains only the possibility that he acquired the infection from the stream in which he bathed.

9 days before his illness. This would fit in with the normal incubation period of 6 to 12 days.

If this were indeed the case, we are faced with the possibility that infected rats exist in Nigeria far removed from towns, so that distribution may be quite general. We may therefore expect to see sporadic cases of leptospirosis quite as frequently in Nigeria as in other countries although, in view of the failure of KIRK (1938) to find the organism in rats in the Sudan, the disease may be absent in the drier parts of the Northern Provinces.

### SUMMARY

1. A case of jaundice with clinical signs resembling yellow fever is described. The results of the agglutination tests would appear to prove that it was a leptospirosis a condition hitherto not definitely proved to exist in Nigeria.

2. The differential diagnosis from yellow fever and other diseases in which jaundice may be associated with fever and urinary changes is discussed.

3. It is suggested that the infection occurred through bathing in a small river in the bush, and that infected rats may be widely distributed throughout Southern Nigeria.

### REFERENCES

- BRUNWICK H (1936) *Trans R Soc trop Med Hyg.*, 30 81  
 DAVIDSON L S P CAMPBELL, R. M., RAE, H J & SMITH J (1934) *Brit med. J* 2 1137  
 GOSZ Y (1933) *Traité de Paris* No 549 (Quoted by VAN RIEL, 1942)  
 GRAY H (1936) *Arch Schiffs- u. Tropenhyg.*, 40 456 (Quoted by Trop. Dis. Bull. 1937 24 358)  
 KADAMER, M & CORTI, E. (1933) *Ann Soc belge Med trop* 13 285 (Quoted by Trop. Dis. Bull. 1934 31 87)  
 KIRK, R (1938) *Trans R Soc trop Med Hyg* 31 667  
 KOLOCHINE EMBE, B & STEFANOUPOULO, G T (1939) *Bull Soc Path exot* 33 919  
 MARTIN SANCHEZ A (1936) *Med Paises calidos*, 9 103 (Quoted by Trop. Dis. Bull. 1939 23 697)  
 NIGERIA (1932) *Ann Rep. of Med Services* 1930 pp 57  
 ——— (1933) *Ibid* 1931, pp 61 71 89  
 ——— (1939) *Ibid* 1937 pp 23 48, 57  
 ——— (1940) *Ibid* 1938 pp 34 44 53  
 SCHÜFFNER, W & MOCHTAR, A (1927) *Zbl Bakt I. Abt Orig* 101 403 (Quoted by Trop. Dis. Bull. 1927, 24 714.)  
 SCHWETZ, J (1933) *Bull Soc Path. exot* 28 1176  
 STROVE R P (1942). *Stall's Diagnosis Prevention and Treatment of Tropical Diseases* 6th Ed Vol 1 pp 362. London H K Lewis & Co Ltd  
 VAN DEN BERGHE, L & VAN RIEL, J (1930) *Bull. Soc Path exot* 23 894  
 VAN RIEL, J (1942) *Revue de Travaux de Sci Méd au Congo Belge* No 1 pp 7

## A FEVER OF THE DENGUE GROUP OCCURRING IN WEST AFRICA.

BY

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The differential diagnosis of febrile illness in tropical Africa is by no means easy. In view of the number of virus and rickettsial infections now known to affect man in Africa, the finding of a few malarial parasites in the blood and the fact that the temperature falls after the administration of quinine can no longer be taken as evidence that a patient has necessarily suffered from malaria and nothing else. Rift Valley fever, Bwamba forest fever and West Nile fever are almost certainly not restricted to Kenya and Uganda. yellow fever may be mild and unattended with jaundice. murine typhus is widely distributed in West Africa and the Belgian Congo while tick-borne rickettsiases also occur in tropical Africa.

Much has been done to differentiate these various febrile illnesses but other infections remain such as disourd in the French Sudan and *fièvre rouge* in the Belgian Congo the true nature of which is still uncertain. In this undifferentiated group must be placed those dengue-like fevers that from time to time have been described in West Africa.

The present communication deals with the investigation of a dengue-like fever seen in West Africa during the past three years.

### DENGUE LIKE DISEASES IN WEST AFRICA.

In 1870 GORE stated that at irregular intervals of time the Colony of Sierra Leone had been visited by epidemics of dengue or broken bone fever which were most severe among Africans. No details are given. A number of references to a disease in some ways resembling dengue is to be found in the *Fourth and Final Report of the Yellow Fever Commission (West Africa)* (1916). In this report MACFIE states that in 1909 he observed three cases of seven days fever occurring in Southern Nigeria at Forcados and Burutu towns within a few miles of one another. Fever continued for from 7 to 9 days the temperature chart being of the saddle back type. There were severe pains in the back,

\* We desire to thank Brigadier R. A. HEPPLE and Col. W. D. ANDERTON for permission to publish these observations and Major W. A. YOUNG, R.A.M.C. for carrying out some of the attempted transmission experiments. Dr. R. D. REID, Senior Pathologist Colonial Medical Service, has most generously placed the resources of his laboratory at our disposal. Our thanks are due also to Dr. A. M. GILLESPIE and Dr. W. A. BOWERMAN for allowing us to refer to patients under their care.



headache, a relatively slow pulse and, in two instances a rubella like rash. There was no albuminuria. BAILEY in 1913 saw a small outbreak among Europeans in Southern Nigeria, while STATHAM, in the same report, mentions a possible case of dengue in Sierra Leone. Attention is also drawn to one case with similar symptoms in the Gold Coast and to two cases occurring at Naraguta in Northern Nigeria in April and November 1913.

The Yellow Fever Commission, in summing up the evidence for the presence of dengue in West Africa, stated that no epidemic of dengue occurred in West Africa "during the period covered by the work of the Commission and in the absence of such a clear indication of the presence of the disease it is advisable to speak with some reserve as to the nature of the cases which have presented signs suggesting such a diagnosis."

Cases in many ways resembling dengue were, however seen in the Gold Coast during the later years of the first World War and are described in the *Report of the Medical Department of the Gold Coast for the year 1920* thus LE FANU (1921) observed six cases in 1917—five European males and one European female were affected and all were probably infected in the European reservation Accra, in the valley between the East and West Ridges. The symptoms in all were similar and consisted of fever for 2 to 5 days, headache, prostration, pains in the loins and shoulder joints and the appearance of a roseolar rash, not unlike measles, chiefly on the body and limbs and appearing on the 1st to 4th day of illness. Reference is also made to a similar case in Accra and one in the Northern Territories seen in 1913. STORRY (1921) referred to two cases occurring at Koforidua in August, 1919 with a profuse measles rash from head to foot except on the palms and soles and on the face where the eruption was not so profuse. WHITE (1921) saw two similar cases in Accra in November 1919—the fever was not relieved by quinine. CONSON (1921) described in some detail cases seen on the outskirts of Kumasi and Accra respectively in January 1918 and October 1920—four other patients, infected in Koforidua, were also seen.

In 1921 DAVIES and JOHNSON reported eighteen cases of a fever of the dengue group in Northern Nigeria—fifteen of the patients were Europeans, three Africans. Fever lasted for from 10 to 13 days and the rash appeared from the 4th to the 6th day of illness. Some at any rate of these cases were quite severe and were almost certainly murine typhus, but as no serological investigations were attempted and no animal inoculations performed the nature of the cases must remain uncertain.

For the next few years there are only scattered references in Annual Medical Reports to dengue like diseases under such names as "Forest fever" and "Koforidua fever" in the Gold Coast or "Benin River fever" in Nigeria. In 1932 and 1937 PURCELL discussed the condition as met with in the Gold Coast where he believed that the infection was restricted to the coastal forest belt.

## A DENGUE-LIKE FEVER IN THE GOLD COAST AND NIGERIA IN 1941-43.

The arrival in West Africa, as a result of the war, of a considerable number of Europeans who had not previously resided in tropical or sub-tropical countries has provided an opportunity for further investigation of the undiagnosed fevers of West Africa. Thus it has been found that murine typhus is widely distributed in all the British West African Colonies and the rickettsiae have been isolated on two occasions in the Gold Coast (FINDLAY et al. 1943, and unpublished observations) and once in Nigeria (YOUNG, 1943).

In addition, a dengue-like fever has been noted in the Gold Coast and Nigeria and certain observations have been carried out on its experimental transmission and on its relation to other African fevers. These are described in the present communication.

## GEOGRAPHICAL AND SEASONAL DISTRIBUTION

The dengue-like fever has not been noted either in the Gambia or in Sierra Leone. In the Gold Coast however it is widespread.

## GOLD COAST

In the autumn of 1941 a small epidemic occurred at Tamale in the Northern Territories among European military personnel. The dates of reporting sick were as follows —

1941—					
21st Oct	Number of cases	3	4th Nov	Number of cases	1
28th		1	11th		1

These persons, although not all attached to the same unit, were living in the same area where there were many mosquitoes and midges *Culicoides* sp., the period being at the end of the rains.

Dr L. GOODMAN informs us that in November 1940 he saw one case in a European at Yendi, 60 miles to the east of Tamale.

Two further cases occurred in Tamale: one a soldier on 2nd May 1942, during the dry season, and a second, an officer, on 8th August 1942, at the beginning of the short rains.

In addition to the Tamale cases others, apparently of a sporadic nature, were seen either among soldiers or civilians in 1942 and 1943 as follows —

Accra	March	Beginning of rains.	Human	July	Rains
Sekondi	March	Beginning of rains	Accra	July	Rains
Koforidua	June	Rains	Accra	August	End of rains
Obuasi	June	Rains	Nsawam	October	Short rains

While Koforidua, Nsawam and Human are all in clearings in the forest and Sekondi is at a point where the forest reaches the sea, Tamale is in savannah country while Accra and its environs are in an open and rather arid plain covered with coarse grassland, not unlike the Northern Territories.

PURCELL (1937) believed that the dengue-like fever is endemic throughout Akum and is to be found from Sunyani in the West to Ho in the East and Aniam in the South. He states however that the disease does not occur in the coastal towns or even in widely cleared areas in the forest such as Kumasi, that it is in fact restricted to the forest. The observations here recorded suggest that the term "forest fever" is unsuitable.

PURCELL also states that the disease occurs not only endemically but epidemically as in 1929 around Oda, at Akrogerri in Ashanti and in the Kpandu-Ho district in the East. The seasonal incidence of the cases seen in the Gold Coast in 1942 agrees with that described by PURCELL, who states that the highest incidence in the south is during the first rains (late March to July) and in September (short rains). In the Northern Territories the disease also seems to occur during or immediately after the first or second rains.

### NIGERIA.

Much less is known of what appears to be the same disease in this colony although sporadic cases have been seen during the past 2 years in Europeans at Enugu Onitsha Province and at Ibadan and Abeokuta. All these towns are in the forest belt. In the early part of December 1942, a small epidemic occurred in a military centre in the forest belt both Europeans and Africans were attacked. A small number of African soldiers were admitted to a Military Hospital with what at first was thought to be German measles. After four Africans had been admitted cases began among Europeans in the barrack area. Five cases were seen in Europeans and later nine other cases in Africans. The dates of onset of these cases were as follows —

Name	Race	Date of Onset 1942	Name	Race	Date of Onset 1942
Pte I O	African	14th Nov	Cpl F	European	17th Dec.
Pte P O		2nd Dec	Pt K. O	African	22nd
Pte A. A.		3rd	Lt. G	European	24th
Lt. W	European	7th			1943.
Major C		8th	Pte W A.	African	4th Jan.
Pte G O	African	8th	Pte R B		6th
L/Cpl A. A.		11th	Pte P D		15th
MSM H.	European	12th	Pte S N		25th
Pte R. A.	African	14th	Pte. S N		5th Feb.

Shortly before and during the period under review five cases of a similar character occurred among the African staff of the General Hospital where all the cases received treatment. The hospital was about 1 mile from the barracks where the bulk of the cases occurred. The respective dates of onset were as follows: 1942, 13th Sept., 19th Dec and 30th Dec. 1943 5th Jan and 19th Jan. The first, second and fifth of these cases did not show any lymph node enlargement and in the fifth case the pyrexia, which was remittent was

prolonged for 12 days. Two further African cases were admitted from units located at distant stations.

On going through the records of the hospital from the date of opening at the end of 1941 only two other patients, Africans resembling those under review were discovered. In 1942 one patient was admitted on 10th July from another barrack area on the same station the other a member of the hospital staff on 13th July. These cases, unlike the remainder thus occurred during the rains. In both these patients there was a rash with pyrexia and some dubious lymph node involvement but as they are not regarded as sufficiently definite they are excluded from the analysis of twenty African cases.

During the period when the disease was epidemic a search was made for *Culicoides* and *Phlebotomus* without success. Mosquitoes were of course present.

### CLINICAL SYMPTOMS

The dengue like fever here described as occurring in the Gold Coast and Nigeria is characterized by fever often of the saddle back type, a measles like rash, enlargement of the lymph nodes, pains in the muscles, bones and joints and a slow pulse.

#### *Europeans*

The clinical symptoms in Nigeria and the Gold Coast are essentially similar though there is considerable variation in intensity. In a few instances the patient is ambulant and complains only of a slight headache and general malaise, followed on the 2nd or 3rd day by the appearance of the rash when the general condition may improve. In cases of moderate severity the temperature remains elevated for 2 to 3 days then falls to normal to rise again after an interval of 24 to 48 hours. In the most severe cases the temperature remains elevated for 6 or 7 days gradually coming down by lysis. The secondary rise in temperature may be absent and is never so high or of such long duration as the primary rise.

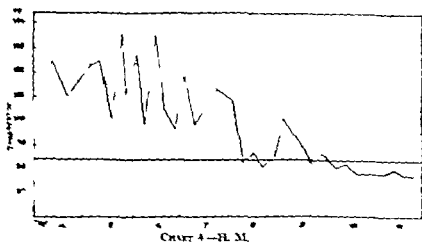
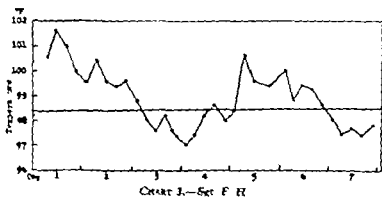
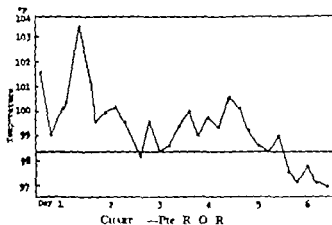
In mild cases the temperature may never reach 100° F. in more severe



CHART 1—Sgt. M. L.

cases it is between 103 and 104° F. Temperature charts are shown. Chart 1 Sgt. M. L. represents a typically mild infection with no secondary rise. Charts 2 and 3 (Pte R. O. R. and Sgt. F. H.) are examples of the febrile

## A DENGUE LIKE FEVER.



reaction in cases of moderate severity in both there is a secondary rise which is seen in typical dengue and in some cases of Rift Valley fever Chart 4 (H M) is from a severe infection and indicates the close similarity in the fever to that of a mild case of murine typhus

After the febrile reaction the most important sign is the occurrence of the rash which appears from the 2nd to the 4th day of illness. It is usually first seen on the forearms and front of the deltoids less commonly on the abdomen and lower part of the chest. It rapidly becomes generalized but is found only to a limited extent on the face. On the arms forearms and legs it is present on both extensor and flexor aspects. The rash takes about 24 hours to reach its maximum and begins to fade as the temperature falls. The rash is of the roseolar type very similar to that of rubella the maculo-papules are discrete and very slightly raised above the surface of the skin usually not more than 1 to 2 mm. in diameter but often they are closely packed together they do not fade on pressure. On the face the rash may present the form of reddish blotches. In very mild cases the rash is the first sign which draws attention to the fact that the patient is not suffering from that only too common complaint in West Africa, a touch of fever but in ambulant cases the rash may scarcely exist for more than 24 hours. The rash not infrequently itches and in at least two Europeans this was a prominent feature. Most of the Africans also complained of itching the rash does not become haemorrhagic. The petechial appearance on the feet noted by PURCELL (1937) has not been observed by us but in one case the skin desquamated in large flakes on the 19th day.

In moderate and severe cases the onset is accompanied by headache usually with a frontal or very rarely post-orbital distribution and vague general muscular aching especially in the back. In mild cases there is no conjunctival congestion and no photophobia but in moderate and severe cases both are not uncommon for the first 24 to 48 hours. There is an absence of coryza or nasal catarrh and no spots appear on the inside of the mouth or pharynx. In more than half the cases observed by us the regional lymph nodes have been palpable and slightly tender enlargement involving the axillary epitrochlear posterior cervical and even the inguinal lymph nodes with the decline in the fever the enlargement of the lymph nodes slowly decreases. In three of the eight cases occurring in Tamale the urine contained a faint trace of albumin during the first 24 to 48 hours. Lack of appetite is common while in three cases there was nausea and in two vomiting. Constipation is common. The spleen and liver are not enlarged and the lungs are normal.

The pulse, as in yellow fever and true dengue is slow sometimes even during the first febrile access with a temperature between 102° and 104° F the pulse rate varies from 80 to 92 a minute. In more than half the cases the pulse rate falls as the temperature falls and during the secondary pyrexia rarely increases. When the temperature finally falls for good the pulse except in a few instances is slow a rate from 56 to 64 is common.

Apart from the headache and backache which to some degree is present in every instance only three cases have specifically complained of pains in the wrists, thumb joints and ankles. In severe cases there may be mental irritability during the first day or two while insomnia is not uncommon. No encephalitic symptoms have occurred either in Africans or Europeans.

#### TYPICAL CASE HISTORIES.

##### EUROPEANS

Lieut. G. developed a temperature of 101° F. with headache and pains all over on 24.12.42. He noted a transient rash on the 3rd day lasting for less than 24 hours. There was no tenderness or enlargement of the lymph nodes and by the 4th day all symptoms had subsided. Some debility persisted for 10 days to a fortnight.

Lieut. W. f. f. tired on 7.12.42 feverish next day and on the 3rd day noted some irritation of the skin. This was followed by a macular rash which was first seen on the arms and rapidly became generalised. At the same time the lymph nodes in the occipital region and groins became slightly enlarged and tender followed by enlargement of the posterior cervical and axillary groups and the epitrochlear glands on both sides. Backache had been present since the 1st day. On the 4th day the hands, right wrist and both ankles became painful. The rash faded on the 6th day by which time the temperature had fallen. It had never exceeded 101.6° F. The joint pains persisted for a further week, and he felt debilitated and suffered from headache for a month or more.

II. M. had returned from leave in England about 4 months before. On 14.9.42 he complained of a frontal headache and general malaise. He carried on for 2 days and then went to bed. On examination of his blood a small number of rings of *Plasmodium falciparum* were found in thick films but administration of quinine was not followed by any fall in the temperature. (Cf. Chart 4.) During the first 3 days of his illness the patient felt extremely irritable and unable to get comfortable. He did not sleep well at night. On the 4th day he complained of headache with pains in the small of the back, in the shins, knees, forearms, wrists and finger joints. The tongue was furred but the pharynx was not congested. There were no spots in the mucous membrane of the mouth and no coryza, though the conjunctivae were slightly suffused. The patient stated that he had previously suffered from malarial and German measles. The posterior cervical, occipital and axillary lymph nodes were just palpable, discrete and slightly tender. On 17.9.42 a faint malarial rash had appeared on the forearms, front of the deltoids and abdomen. Twenty-four hours later the rash was more marked, maculopapules 1 to 2 mm. in diameter covering the whole of the trunk, legs and arms. On the face the rash was much less distinct. The lesions were slightly raised but did not fade on pressure. As the temperature fell the rash regressed and by the 10th day had almost gone. During convalescence the patient became easily played out and tired for about a month after the temperature had returned to normal.

##### AFRICANS

The symptomatology in Africans based on an analysis of twenty cases is very similar to that in Europeans.

Pyrexia. Generalised was one of the initial complaints in every case but two. In twelve cases its duration did not exceed 3 days initially and in a further five did not exceed 6 days. In one case there was pyrexia for 9 days and in another remittent pyrexia lasted for 12 days. In general however, the temperature was not of the remittent type. The highest recorded figure was less than 100° F. in six cases between 100 and 102° F. in eleven cases and more than 102° F. in three cases. Recrudescences of pyrexia occurred in three cases. The respective rises were to 104° F. on the 7th day after 4 hours normality to 107° F. on the 4th day after 2 days normality and to 105.6° F. on the 8th day after

3 days' normality. In each instance the secondary rise was higher than the initial one and in two cases coincided with the appearance of the rash, suggestive of true dengue.

The pulse rate was not increased in proportion to the rise in temperature.

**Rash.** The eruption was macular or coarsely papular. It was accompanied by irritation and was first noticed on the forearms. From here it rapidly spread to the trunk and lower limbs. The dorsal and ventral aspects were affected, but on the face the erythema was either only slight or was absent. In fourteen cases it appeared on the 1st or 2nd day, in five cases on the 3rd or 4th day and in one on the 7th day. It lasted for 3 days or less in sixteen cases for 4 days in one case and for 6 days in another and was not followed by staining or desquamation. In the remaining two cases however the rash instead of subsiding, became lichenified, especially on the back. This condition persisted for some time after the patients had left hospital.

**Lymph node involvement.** Enlargement of lymph nodes was present in sixteen cases. The size of individual nodes did not greatly exceed that of a cherry stone. They were discrete, firm and usually tender at the outset. The enlargement persisted longer than any other of the clinical features, usually continuing for a week or more after discharge from hospital. The axillary group was most frequently involved (fourteen cases), next was enlargement of the epitrochlear lymph nodes (eight cases), sometimes on one side only. The occipital lymph nodes were enlarged in seven cases and the cervical in a similar number. Involvement of the lymph node in the groin was indicated in several patients by the sudden onset of tenderness, but as these lymph nodes are usually enlarged in the African from other causes it is not possible to assess accurately the frequency of involvement. Spleenic enlargement did not exceed that found in Africans in general either in incidence or degree.

**Pains.** A number of patients complained of body or limb pains of some severity. Most characteristically these were in the medium sized joints of the limbs—the ankles, knees or elbows (seven cases). There was pain on movement but no perceptible swelling. In two cases the complaint was of pains all over. Three further cases had pain in the chest, the neck and the soles respectively. Backache was never specifically mentioned and eight cases made no complaint of pain at all. The pains seemed to be related to the onset of the rash in several cases. Pain in the eyes was not met with; there was some conjunctival suffusion in four cases. Headache accompanied the pyrexia in certain cases but was not severe.

**Local manifestations.** These were conspicuously absent. Two cases in response to a leading question stated that they had slight nasal catarrh, but there was no objective evidence of this nor in any of the cases was there complaint or evidence of sore throat. One patient had petechial spots on his palate and another a small ulcer in the same situation probably arriving from another cause. In one case there was slight diarrhoea at the onset and in another diarrhoea occurred during a secondary rise of temperature on the 8th day. There was no gastro-intestinal disturbance in any other case.

## COMPARISON OF THE DISEASE IN EUROPEANS AND AFRICANS

While the majority of the features are similar in the two races, minor divergencies occur. The disease has been rather more severe in the Europeans and a greater degree of debility has followed. The rash has appeared later (the 3rd day to the 6th day). Moreover backache, not mentioned by the Africans, was a prominent feature in certain of the Europeans.

**Blood changes.** The blood does not show any marked changes either in Africans or Europeans in the total number of red blood corpuscles while the total number of leucocytes has varied from 4,400 to 8,000 per c mm. By the 4th day there appears, however, to be a slight increase in the percentage of lymphocytes. Thus H. M., on the 4th day of illness, showed polymorphonuclear



leucocytes 62 per cent., small lymphocytes 32 per cent. mononuclears 5 per cent. eosinophils 1 per cent. Lieut. A S on the 5th day showed a total leucocytosis of 8,000 per c.mm. polymorphonuclear leucocytes 38 per cent. small lymphocytes 51 per cent. mononuclears 7.5 per cent., eosinophils 3.5 per cent. One African showed a relative lymphocytosis of 70 per cent with a total leucocyte count of 4,600 per c.mm. No case has proved fatal and in all convalescence has been uneventful.

#### EXPERIMENTAL INVESTIGATIONS.

Efforts to grow bacteria from the blood by culture in a variety of media both under anaerobic and aerobic conditions proved ineffective.

Blood from eight cases was examined at various stages of convalescence for evidence of agglutinins to *Proteus* OX19 OX2 and OXK with negative results. Agglutination reactions for typhoid and paratyphoid organisms were negative and in eight Africans in whom the Ide reaction was performed it was, surprisingly negative in all.

Blood was removed from 5 patients on the 1st or 2nd day of the appearance of the evanthem and was injected into a variety of animals by numerous routes. When it was not possible to carry out animal inoculations immediately all specimens of blood were placed on ice in a thermos flask.

White mice were inoculated intracerebrally and intraperitoneally without causing any illness during the ensuing month. Mice killed 4 to 8 days after inoculation showed no rickettsiae in smears from the spleens.

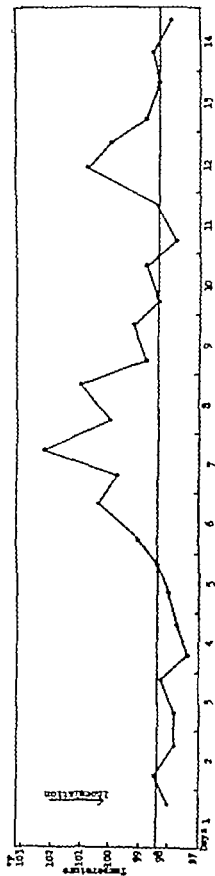
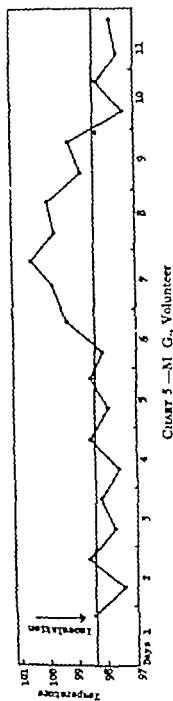
Guineapigs were inoculated intraperitoneally with whole blood and with clot washed in saline as is done in isolating rickettsiae. No thermal response occurred in any of the animals during the ensuing 4 weeks. Guinea pigs were also inoculated subcutaneously. No enlargement of the regional lymph nodes was seen while intracerebral inoculation was not followed by the development of any symptoms.

Rabbits and bush rats, *Cricetomys gambianus* injected intraperitoneally also failed to show any symptoms.

The following species of monkey were injected intracerebrally with serum, *Erythrocebus patas* *Cercopithecus aethiops sabaeus* *C. mona lower* and *C. diana rolorev*. None of these monkeys showed any untoward symptoms. A baboon, *Papio anubis charas* received a subcutaneous injection of whole blood.

Two explanations of this failure to infect animals are possible. either the causal agent, probably a virus, disappears from the blood by the time the rash has appeared or the animals inoculated were not susceptible to the causal agent.

In these circumstances an attempt was made to transmit the disease to man. In the Gold Coast two volunteers, Africans, each received 1 c.c. of serum removed from A. S. on the 1st day of the appearance of the rash, the 2nd day of fever. The serum was injected subcutaneously in the arm.



TEMPERATURE CHARTS OF TWO VOLUNTEERS  
inoculated with serum from case of dengue-like fever

In both volunteers a rise in temperature took place on the 5th day after inoculation, the temperature rising to 99.4 and 99 F respectively (Charts 5 and 6). In M. G. (Chart 5) the temperature was above normal for 4 days and there was no second rise of temperature. In Y. A. (Chart 6) the highest temperature also occurred on the 2nd day of the reaction the 6th day after injection. In this case however the temperature was of saddleback type and did not return to normal for 9 days. In M. G. there was a slight rash on the abdomen for about 24 hours, but Y. A. showed a raised morbilliform rash chiefly on the arms, abdomen, chest and legs. This rash was seen on the 2nd day of fever but the date of its disappearance was not easy to determine owing to the patient's dark colour. Both patients complained of headache and of aches and pains in the limbs and back but they were not incapacitated.

Blood was removed from Y. A. on the 7th day after inoculation, and the 3rd day of fever. 1 c.c. was injected subcutaneously into a third volunteer O. J. On the 5th day the temperature rose to 99° F in the evening on the following morning it was 98° F rising again to 99.6° F in the evening thereafter the temperature remained normal. It is possible that this patient was partially immune to the infection. Two Africans inoculated with blood in Nigeria showed no reaction of any sort. The blood was removed on the 5th day of illness. Later blood was removed from a patient on the 3rd day of fever 24 hours after the appearance of the rash and inoculated subcutaneously into two volunteers without result. The causal agent may have disappeared from the blood after the first 2 days or the volunteers may have been immune. In this connection blood taken from a patient with classical dengue, contracted in the Middle East, on the 7th day of fever failed to cause fever or any reaction when injected into two volunteers.

PURCELL (1937) mentions that a second attack may be mild with only a transitory exanthem. In one patient seen by us in the Gold Coast during an ambulant attack similar but more severe symptoms were said to have occurred 3 years previously.

#### THE RELATIONSHIP OF THE DENGUE LIKE FEVER TO OTHER DISEASES.

The disease which has been described in the Gold Coast and Nigeria obviously resembles classical dengue in its clinical symptoms in that it is characterized by fever sometimes of the saddleback type an exanthem and vague pains in the joints and limbs. It also agrees with classical dengue in the fact that it can be transmitted to man, the incubation period, 5 days, being within that usually described for dengue. In addition, like dengue the infection is not transmissible to laboratory animals.

In dengue the definite rash generally appears during the second febrile rise. In two African cases the secondary rise of temperature coincided with the appearance of the rash. There was no evidence of a primary rash rapidly

fading and separated from the secondary rash. In only one European case was anything like the true break-bone pain noted in the wrist and thumb joints. In classical dengue enlargement of the lymph nodes is not a characteristic feature. Unfortunately owing to the lack of any specific test, there is no conclusive evidence that what has been described as dengue in different countries is always the same infection. There is in fact some evidence to suggest that the name dengue has from time to time been applied to what are in reality different diseases but in the absence of experimental animals other than man the laboratory investigation of the dengue-like fevers is not easy. It is thus possible that in West Africa more than one dengue-like fever may be present.

One infection which bears a close similarity to the dengue-like fever of West Africa here described is the *fièvre rouge* of the Belgian Congo. CECCALDI (1941) has recently reported a very similar condition in French Moven Congo.

There is no evidence to link the dengue like fever of West Africa with the rickettsial infections with which on clinical grounds severe cases might possibly be confused. Failure to infect guineapigs or to produce a positive Weil-Felix reaction in the serum serves to differentiate it from murine typhus or tick borne typhus while the absence of rickettsiae in smears from the spleens of guineapigs or mice rules out Q fever.

The presence of a rash and of slight swelling of the regional lymph nodes might lead to confusion with measles or with rubella. Coryza or Koplick spots however are not seen in the West African dengue-like fever although in the Twi language the same term 'ntobro' is used to include measles, rubella and the fever here discussed.

The clinical symptoms characteristic of this dengue-like fever are however those seen in many virus infections and the probability of a virus causation is increased by the failure to cultivate bacteria from the blood.

In view of the similarity to other virus infections, it appeared to be of interest to determine whether sera from patients recovered from the West African dengue-like fever showed any capacity to neutralize certain other viruses isolated in tropical Africa. Experiments were therefore carried out with the viruses of Rift Valley fever, Bwamba forest fever and West Nile fever.

Bwamba forest fever was first described by SMITHBURN, MAHAFFY and PAUL (1941), West Nile fever by SMITHBURN *et al* (1940) both in Uganda. Rift Valley fever was first noted in 1931 by DAUBNEY, HUDSON and GARNHAM in Kenya.

Both West Nile fever and Rift Valley fever are now known not to be restricted to the countries where they were originally described.

Our thanks are due to Dr W. A. SAWYER, Director of the International Health Division of the Rockefeller Foundation for the viruses of West Nile fever and Bwamba forest fever. These viruses, after coming from New York to London by air were inadvertently flown to Russia eventually however they arrived in West Africa and were still virulent for mice.

Mice which had been inoculated intracerebrally and intraperitoneally with serum from patients suffering from the dengue like fever were subsequently found to be as susceptible to the viruses of Rift Valley fever West Nile fever and Bwamba forest fever as normal mice.

Hyperimmune sera were next prepared in *Cercopithecus* monkeys against the viruses of West Nile and Bwamba forest fevers one of us (G. M. F.) provided the Rift Valley fever immune serum.

Saline suspensions of mouse brains were prepared in dilutions of from  $10^{-2}$  to  $10^{-6}$  and mixed with equal amounts of serum from patients recovered from the West African dengue like fever with serum from the hyperimmune monkeys and with normal serum. The mixtures after standing at  $37^{\circ}\text{C}$  for 2 hours were inoculated intracerebrally into mice. No virucidal action was shown by the serum from patients recovered from the dengue like fever. A similar experiment was carried out with Rift Valley fever virus the injections being made intraperitoneally instead of intracerebrally. Here again no virucidal action was shown by serum from patients recovered from the dengue like fever seen in West Africa.

#### CONCLUSIONS

1. A dengue like fever is described in Nigeria and the Gold Coast it occurs sporadically and in small epidemics and is not confined to the forest zone. It has been seen both in Europeans and Africans.

2. The symptoms of the disease are fever of from 2 to 10 days duration, often of the saddleback type vague muscular bone and joint pains, enlargement of the regional lymph nodes and a measles like rash coming out from the 2nd to the 6th day of illness.

3. The infection has not been transmitted to the following species of monkey *Papio anubis choras* *Cercopithecus oethiops sabaeus* *C. mona lowei* *C. diana roloway* and *Erythrocebus patas* or to mice, rabbits, guinea-pigs or bush rats *Cricetomys gambianus*.

4. The disease was reproduced in two volunteers by subcutaneous injection of serum after an incubation period of 5 to 6 days, but in four other volunteers no reaction occurred.

5. No organisms could be cultivated from the blood it is suggested that the disease is due to a virus.

6. The serum of convalescent patients contains no virucidal anti bodies against the viruses of Rift Valley fever Bwamba forest fever and West Nile fever.

7. The relationship of the disease to classical dengue, fièvre rouge and other infections is discussed.

## REFERENCES

- BAILEY J C M. (1916) Seven days fever *Fourth and Final Report Yellow Fever Commission (West Africa)* p 18 London J & A. Churchill.
- CECCALDI J (1941) Fièvres exanthématiques *Rapport sur la fonctionnement technique de l'Institut Pasteur en 1940* p 45 Brazzaville Afrique française libre
- CORSON J F (1921) *J trop Med* 24 253
- DAUBNEY R. HUDSON J R. & GARNHAM P C (1931) *J Path Bact* 34 545
- DAVIES L. W. & JOHNSON W B (1921) *J trop Med* 24 189
- FINDLAY G M. REID R. D. & MACGRAITH B G (1943) *J R. Army med Cps* 80 134
- GORE, A. A. (1870) *Annual Report to accompany the return of sick and wounded of the troops stationed at Sierra Leone for the year ending 31st December 1869*
- LE FANU C. V. (1921) Dengue and dengue like fever *Report on the Medical Department for the year 1920* p 59 Gold Coast Government Accra.
- MACFIE, J W S (1916) Seven days fever *Fourth and Final Report Yellow Fever Commission (West Africa)* p 17 London J & A. Churchill
- PURCELL, F M. (1932) *W Afr med J* 6 6
- (1937) *Trans R Soc trop Med Hyg* 30 541
- SMITHBURN K. C. HUGHES T P. BURKE, A. W. & PAUL, J H (1940) *Amer J trop Med* 20 471
- MAHAFFY A F & PAUL, J H (1941) *Ibid* 21 75
- STATHAM J C. B. (1916) Dengue *Fourth and Final Report Yellow Fever Commission (West Africa)* p 10 London J & A. Churchill
- STOREY F H (1921) Dengue and dengue like fevers *Report on the Medical Department for the year 1920* p 58 Gold Coast Government, Accra
- WHITE, R. O (1921) *Ibid* p 58
- YOUNG W A. (1943) *Unpublished observations*

may progress satisfactorily until the products of incomplete carbohydrate metabolism begin to appear in the milk of nursing women after the ingestion of these metabolites the infantile body tries to get rid of them through further oxidation to their end-products but this of course, is only possible if sufficient vitamin B is available. As every infant born alive probably has a reserve (however small) of this vitamin, the toxic action is delayed until this reserve is depleted. It is, however immediate when the organism is already avitaminotic.

Apparently the amount of toxic substance in the milk of avitaminotic women is far beyond the infantile tolerance. GUERRERO and QUINTOS (1910) having reported a case in which two breast feeds proved fatal to an infant. This infantile intolerance would explain the extreme acuteness of infantile beriberi. Obviously the acuteness of the symptoms will depend on the amount of milk ingested—this fact explains why acute infantile beriberi is most frequently encountered in overfed infants. In China male infants are apt to be overfed more frequently than female—the predilection of the Chinese for male children accounts for this—and this may be the main reason for the higher incidence of infantile beriberi in males.

Since, as stated above infantile beriberi can be produced by human milk after even a few feeds, the writer has suggested that instead of saying "infantile beriberi occurs in breast fed infants only" it would be more correct to say that "infantile beriberi occurs only in infants who have been, at some time breast fed" (FEJELY 1941b).

At first sight it would seem incomprehensible that infants born of B avitaminotic women, and fed since birth on vitamin B deficient food other than human milk, should not show signs of beriberi. Frequently it is observed that artificially fed infants with symptoms of anorexia, constipation and retarded growth improve immediately after the administration of vitamin B proving that such infants were suffering from B hypovitaminosis. Logically it would follow that such infants if unmedicated should develop in due course beriberi, although not of the infantile but of the adult type. This absence of beriberi is all the more surprising as we know that vitamin B is even more essential for growth than for maintenance and that the caloric requirements of infants are relatively greater than those of adults and that finally in the case of infants, these calories are derived mostly from carbohydrates (according to WILLIAMS and SEIZ 1938 vitamin requirements are in direct proportion to the intake of non-fat calories). The writer has suggested that the explanation for this absence of adult type of beriberi in artificially fed infants may lie in the fact that such infants succumb to intercurrent infections before their B avitaminotic condition manifests itself in beriberi of the adult type.

As already stated, methyl glyoxal has been found in all the body fluids—cerebrospinal fluid, urine, blood, and milk—of avitaminotic beings. It follows that methyl glyoxal possibly may appear in all the organs and tissues of such beings. In syphilis, as well as in malaria, the protean manifestations of the

disease are attributed to the localization of the infection—the organs or tissues most affected giving rise to signs and symptoms which dominate the clinical picture. It is also possible that the same explanation may be applied in the case of infantile beriberi and that the clinical picture varies according to the organs and tissues with the greatest concentration of toxic metabolites. This would explain many apparently contradictory statements made by authors on infantile beriberi. Thus for example the oedema is sometimes described as renal and sometimes as cardiac the convulsions sometimes as clonic and sometimes as tonic the behaviour of the reflexes sometimes as characteristically diminished or absent and sometimes as absolutely inconclusive. This would also explain the different reactions of the organism to the same vitamin B<sub>1</sub> deficient food—thus in experimental animals it sometimes produces polyneuritis and sometimes beriberi and human beings react either with dry wet or cardiac beriberi. There would also be an explanation for the rather constant enlargement of the right ventricle since this part of the heart is the first to receive from the digestive organs blood still rich in toxic metabolites.

According to symptoms and course infantile beriberi may be classified as follows —

#### INITIAL INFANTILE BERIBERI

vomiting restlessness, pallor flabbiness anorexia, insomnia, meteorism

#### SUBACUTE INFANTILE BERIBERI

vomiting puffiness, oliguria, meteorism  
abdominal pain dysphagia, aphonia  
tonic convulsions diarrhoea.

#### ACUTE INFANTILE BERIBERI

cyanosis dyspnoea, running pulse

#### CHRONIC INFANTILE BERIBERI

vomiting loss of weight, retarded  
growth inanition anaemia head re-  
traction aphonia oliguria oedema,  
constipation meteorism

Mixed forms are often observed such as initial or subacute infantile beriberi with early signs of cyanosis dyspnoea and tachycardia. The condition of the reflexes is variable—they may be exaggerated, normal diminished or absent consequently only the last two mentioned conditions may be of diagnostic value.

In all stages of infantile beriberi secondary infections especially those of the respiratory tract, are frequently present. In fact bronchitis is usual and consequently this disease and the pyrexia caused by initial bronchopneumonia or other complications are regarded by some authors as symptoms of infantile beriberi. In uncomplicated cases the temperature is normal or even subnormal.



The mortality in infantile beriberi is extremely high. According to the Manila health authorities it amounted to approximately 94 per cent. before the introduction of specific treatment (extract of rice polishings), whereas HARMAS (1937) reported that the mortality of treated infantile beriberi cases, in a series of 322 admittances, amounted to 45.43 per cent.

Unfortunately the writer was not afforded the opportunity of performing autopsies herself hence she uses the finding of authors in the Philippines, Dutch East Indies and Japan. According to them the most striking feature in cases of uncomplicated infantile beriberi is the absence of any pathological findings to account for death. There is, in varying degree, enlargement of the right ventricle and slight effusions in the pleural pericardial and abdominal cavities. In addition there may be oedema or congestion of the liver spleen and kidneys, thickening of the gall bladder and oedema of the brain and lungs. However intercurrent diseases such as intestinal catarrh bronchitis and bronchopneumonia are very common and obscure the picture. These pathological findings show that although external oedema is unusual and even when present, not very marked, internal anasarca is frequently encountered. This anasarca includes not only pleural, pericardial and peritoneal effusions, but oedema of the brain, lungs, liver spleen, kidneys and heart (according to AALSMEER and WENCKEBACH 1928, the enlargement of the right ventricle does not represent a real hypertrophy but only an oedema of the sarcoplasm). Furthermore it seems that this anasarca is specific and not merely the result of cardiac insufficiency.

As can be seen from such postmortem findings, when infantile beriberi is not suspected the cause of death may be either not established or attributed to the above mentioned complications. Admittedly the pathological findings in infantile beriberi are similar to those of adult beriberi, especially the cardiac type. In adult cases, however these findings are more constant furthermore there may be marked oedema (in case of wet beriberi) or degeneration of the nerves with atrophy of the corresponding muscles (in cases of dry beriberi). Moreover in adult beriberi the clinical diagnosis and the history of the illness prior to death may be of benefit for a proper diagnosis, whereas in infantile beriberi neither the clinical diagnosis nor the history may be available (because dead babies are often dumped on the streets) or the parents may report that "the child suddenly turned blue and died" or "the child was frightened got convulsions and died". Obviously such a history is not helpful in addition the fact that the child is frequently of a well-nourished appearance without any outward signs of disease is very confusing and has even given rise to suggestions of accidental poisoning or foul play.

Women with manifest signs of beriberi (such as numbness, weakness of the extremities, oedema, absence of knee jerks, etc.) may nurse infants having no apparent signs of infantile beriberi and vice versa—seemingly healthy women may be nursing infants with manifest signs of this disease. Apparently such

women and infants with no manifest symptoms are still in the latent stage cases have been reported (ALBERT, 1931) where women developed manifest beriberi weeks after their infants had died of infantile beriberi

It is interesting to note that latent infantile or maternal beriberi may become manifest even after the administration of vitamin B<sub>1</sub> to the nursing mother. A possible explanation may be the insufficiency of the amount of vitamin administered. In the writer's experience, it is necessary to give initial doses of 50 mg per day to obtain immediate results but unfortunately this was not always feasible owing to economic and other factors.

As has been mentioned already the manifestations of infantile beriberi are extremely diverse and multiple. Secondary infections are common and may appear in the latent and initial stages thus adding to the vast number of differential diseases. Consequently in the discussion of differential diseases the writer will limit herself to those which have been encountered most frequently in her experience as an Infant Welfare Officer in Hongkong.

The differential diagnosis will be discussed according to the classification made earlier in this paper.

#### INITIAL INFANTILE BERIBERI

##### *Differential diagnosis*

*Overfeeding* the chief complaint is vomiting after feeds the child is overweight there are no physical signs of disease. Enquiry often reveals that the infant is fed hourly during the day and a few times during the night. The physician orders a limitation and regulation of feeds but vomiting does not cease. Air swallowing is suspected the method of expulsion of gas from the stomach is demonstrated to the mother and some medication against acidity may be prescribed. The vomiting persists but the physician is not alarmed. The child is in excellent physical condition, there is very little or no loss of weight the amount of food vomited is insignificant and consists mostly according to the mother of mucus (Some of the mothers complain only of retching in infants with no loss of food whatever). The physician may then suspect infantile neuropathia but still is not alarmed. However next day or soon after he is amazed to learn that the child has died. It is always disclosed that death has been sudden the child turned blue and died or was found dead in bed, or strapped to the mother's back (a common method of carrying a child while at work).

In cases of persistent vomiting in infants fed on breast milk, without physical signs of any disease infantile beriberi should be suspected. The medical history of other children (living or dead) the diet of the mother during pregnancy and lactation and the existence of symptoms of maternal B<sub>1</sub> avitaminosis may confirm the diagnosis of infantile beriberi.

*Status lymphaticus* another complains that the baby is getting "soft". The

child is fat, pale and flabby and there may be enlargement of the heart and early signs of cyanosis and dyspnoea. However the absence of enlarged tonsils of palpable superficial lymphatic glands and of an enlarged thymus as well as the history maternal avitaminosis and diet should indicate the real nature of the illness.

*Bronchitis* mother complains that the infant has a lot of mucus in his throat, is peevish and restless, does not sleep well cries a lot is vomiting and has no voice. On examination signs of bronchitis and slight fever may be detected and most of the above mentioned symptoms may be attributed to these conditions, whilst the hoarseness or aphonia may be attributed either to strain from crying or to suspected laryngitis. However the history the enlarged right ventricle the maternal diet and avitaminosis may indicate infantile beriberi. The aphonia in infantile beriberi is rather characteristic and may result in the so-called "visible cry" the mouth is open, there are crying grimaces but no sound is heard. In cases of aphonia marked oedema of the larynx may be present (even necessitating tracheotomy), and degeneration of the recurrent laryngeal branch of the vagus may be found on postmortem examination. In the writer's experience the aphonia disappears promptly if vitamin B is administered in the initial stage and a similar result is frequently obtained in the subacute stage whereas in the chronic stage the aphonia may persist for weeks and months even after the disappearance of all other symptoms of infantile beriberi. This would indicate that though the aphonia in the initial stage is caused by oedema in the chronic stage it is probably caused by paralysis and in the subacute stage by either or both of these causes. Moreover the common complaint of "mucus in the throat," referred to as "increased salivation" by some authors, may be the result of such oedema in the respiratory tract. This oedematous condition of the respiratory organs in infantile beriberi may be also the main cause of the high incidence of secondary infections in these organs, which infections frequently appear not only in the initial but even in the latent stage.

#### SUBACUTE INFANTILE BERIBERI

##### *Differential diagnosis*

mother complains that the child has green diarrhoea, abdominal wind (an ominous sign), is restless, vomits and has no casts. Inspection reveals an overweight infant with recent loss of weight the abdomen possibly being slightly distended on palpation. In the majority of cases the child is strictly fed, feeds are given irregularly and much too frequently. However absent knee jerks, enlargement of the liver and of the right t, tachycardia, the characteristic aphonia and other symptoms of infantile beriberi. The maternal diet during the period

of pregnancy and lactation as well as signs of maternal B<sub>1</sub> avitaminosis may further confirm the diagnosis.

A short period of starvation leads to an immediate improvement of the condition as the more acute symptoms promptly disappear—only to reappear again as soon as an appreciable amount of maternal milk is ingested. This procedure may be repeated with the same result and the mother may even remark that her milk must be bad as one or more of her breast fed infants have died of an identical disease. Frequently such mothers insist on weaning their infants. In such cases the acute symptoms disappear even before the introduction of specific treatment although there remains the danger of a fatal enteritis as a result of infantile avitaminosis dyspepsia and unhygienic methods of food preparation. The best results may be obtained through a temporary cessation of maternal feeding (during which time albumin water or similar preparations may be given) while both mother and infant should undergo vigorous treatment with specific vitamin.

*Meningitis* there may be rigidity of the neck and extremities reflexes may be exaggerated at first and absent towards the end there may be strabismus and a history of clonic convulsions as well as fever. Normal pressure and clarity of cerebrospinal fluid absence of bulging fontanelles and absence of Kernig's sign would be indicative of infantile beriberi. In addition the history the maternal diet and avitaminosis would serve for further confirmation.

*Nephritis* the puffiness of the face hands and feet as well as a complaint of oliguria or anuria would suggest this condition. However the absence of albumin in the urine (slight albuminuria may occur in the terminal stage due to congestion of kidneys), diminished or absent knee jerks aphonia and other symptoms as well as the history maternal diet and avitaminosis would indicate infantile beriberi. Of most diagnostic value is the therapeutic test administration of vitamin B<sub>1</sub> is followed by profuse urination and considerable loss of weight.

*Peritonitis* the presence of a gastro-intestinal syndrome such as vomiting diarrhoea, abdominal pain meteorism and tenderness of the abdomen as well as pyrexia may suggest this condition. The history the presence of other symptoms e.g. enlarged right ventricle oedema, etc., and the subsequent course as well as the maternal diet and avitaminosis should point to the true condition.

*Helminthiasis* this infection is common in Hongkong even amongst breast fed infants probably due to the widespread use of "comforters" and their unhygienic handling. The above mentioned gastro-intestinal syndrome and the absence of fever may suggest this condition but the other symptoms suggestive of infantile beriberi may lead to a correct diagnosis.

*Tetany* carpo-pedal spasms and oedema of the hands and feet may suggest this condition. However the fact that spasmodophilia is extremely rare in Hongkong (probably due to perfect assimilation of calcium) the history of

strict breast feeding, the absence of Chvostek's, Lust's and Hoffa's signs should exclude this condition.

*Cerebral injury* mother may report that the infant got "fits" (convulsions) after a fall. Absence of external injury tachycardia, enlarged right ventricle and liver aphonia and other symptoms may indicate infantile beriberi. Experience shows that Chinese women often attribute sudden attacks of disease to "frights" which, they claim, are caused either by falls, loud noises, or by seeing evil spirits.

*Diphtheritic paralysis* dysphagia, aphonia strabismus, absence of knee and ankle jerks and symptoms of circulatory insufficiency may suggest this condition. The absence of previous diphtheritic infection, the nutritional state of the infant, non-occurrence of any definite paralysis in the extremities and the maternal diet and maternal avitaminosis may indicate infantile beriberi.

#### ACUTE INFANTILE BERIBERI

This form of the disease is known to Chinese in Hongkong as "*fung taam*" (wind-mucus), which is a dreaded infantile scourge and one of the main causes of death in infants. As can be seen the name is appropriate, inasmuch as it is comprised of the two symptoms most frequently referred to by the masses who believe that "wind drives mucus into the throat thus causing suffocation."

#### Differential diagnosis

*Bronchopneumonia* this disease may be suggested by a sudden attack of cyanosis and dyspnoea after a few days of simple cough physical signs (crepitations, etc.) may be absent, but then they are not always easily discernible in infants. There may be pyrexia of varying degree the temperature may be normal—afebrile bronchopneumonia being suspected or the temperature may be subnormal—early cardiac failure being accepted as the cause. In all cases of suspected afebrile bronchopneumonia (which is extremely rare in well nourished infants), infantile beriberi should be suspected where such disease is endemic. Absence of physical signs, absence of knee jerks as well as enlarged right ventricle and liver the history the maternal diet and avitaminosis should suggest infantile beriberi. As already mentioned bronchopneumonia is one of the most frequent complications and may appear even in the latent stage of infantile beriberi. In addition, pulmonary oedema is encountered (as part of internal asystolia) in a certain proportion of cases. These two latter complications may obscure the picture and make the diagnosis of primary infantile beriberi extremely difficult and at times, impossible.

*Cardiac disease* cyanosis and dyspnoea, enlarged heart and tachycardia may suggest this condition. Enlargement of the right ventricle only absence of murmurs as a rule absence of cyanosis from birth and the history would exclude congenital, post-infectious and idiopathic heart diseases. The absence

of knee jerks maternal diet and avitaminosis may further indicate infantile beriberi

*Laryngeal diphtheria* a pediatrician informed the writer that general practitioners frequently sent him cases alleged to have laryngeal diphtheria with requests for tracheotomy when neither false membrane nor inflammation of larynx was found. The history of previous aphonia pyrexia, sudden cyanosis and dyspnoea may give rise to a mistaken diagnosis, especially when the presence of infantile beriberi is not even suspected. The absence of inflammation and false membrane in the pharyngeal and laryngeal regions, the absence of knee jerks the maternal diet and avitaminosis may indicate infantile beriberi

*Asthma thymicum* status lymphaticus may be aggravated by an enlarged thymus with subsequent attacks of cyanosis and dyspnoea. These attacks as well as the pale and flabby appearance of the infant in general are very similar to those observed in infantile beriberi. The absence of enlarged tonsils cervical glands and thymus negative knee jerks and other symptoms as well as the maternal diet and avitaminosis may exclude asthma thymicum

*Bronchitis* in the course of this complaint sudden cyanosis and dyspnoea may appear as a result of obstruction in the respiratory tract. Enlargement of the right ventricle and liver the absence of knee jerks, the history and the maternal diet and avitaminosis may indicate acute infantile beriberi.

*Accidental poisoning* until 1939 when the real cause of *fung toan* was pointed out (Fehly, 1940) sudden deaths in well nourished well fed and apparently healthy babies and the absence of any pathological findings to account for such deaths baffled physicians in Hongkong. Two theories of accidental poisoning were advanced one—the possibility of inhalation of poisonous fumes from charcoal stoves because women often have infants strapped to their backs while cooking the other—poisoning with Chinese medicine administered for some minor ailment (e.g. bronchitis). Confirmation of the latter theory seemed to be supplied by the pungent smell exhaled by many of the affected infants and the statements of the mothers that the infants had been given medicine supplied by herbalists. Actually the medicine generally consists of an extract of garlic, which is also prescribed as native treatment for adult patients with beriberi

*Laryngismus stridulus* a sudden attack of cyanosis and dyspnoea in an apparently healthy infant may suggest this condition. The absence of "crowing" negative Chrostek's sign the history the course of the disease an enlarged right ventricle and tachycardia negative knee jerks as well as other symptoms may suggest infantile beriberi

#### CHRONIC INFANTILE BERIBERI

Infants in this stage are either on mixed feeding (possibly since birth) or they are entirely artificially fed having previously been breast fed. As a result, the symptoms of intoxication may have already disappeared the clinical

picture being dominated by symptoms of B avitaminosis such as retardation of growth anorexia constipation, etc. It is interesting to note that retarded growth may be the only sign present one frequently encounters 10 months old infants weighing 7 to 8 lb showing 2 to 4 teeth and being apparently healthy but for their apathetic facial expression.

Obviously when toxic symptoms are absent, chronic infantile beriberi is similar to the B hypo- or a-avitaminosis of infants who have never been breast fed the difference being only one of degree.

### *Differential diagnosis*

*Malnutrition* conditions arising mainly from a quantitative or qualitative deficiency of one or several food elements may produce a picture similar to chronic infantile beriberi e.g., undernourishment, infantile scurvy vitamin A deficiency and nutritional oedema (judging from clinical and radiological evidence vitamin D deficiency is practically unknown in Hongkong). Enquiry into the nature and amount of food given, absence of signs of vitamin B (other than B<sub>1</sub>) deficiency as well as the absence of haemorrhages, hyperkeratosis, xerophthalmia and the presence of an enlarged right ventricle, tachycardia, negative knee jerks aphonia, etc. will indicate infantile beriberi.

The diagnosis of primary disease is sometimes difficult if chronic infantile beriberi is associated with vitamin A and C deficiencies (not uncommon in Hongkong). In cases where such multiple vitamin deficiencies are obvious, marked improvement frequently follows the administration of vitamin B alone. Consequently the question arises as to whether such vitamin A and C deficiencies are caused by a lack of these vitamins in the diet or by their imperfect assimilation. It is only reasonable to presume that in chronic infantile beriberi digestion and assimilation are impaired as a result of repeated intestinal catarrhs and of the diminution of gastric and pancreatic secretions (BARKIN 1933 SURK, KIK and BUCHANAN 1935).

*Tuberculosis* the appearance of the infant and a loss of weight may suggest this condition. Negative X rays and tuberculin tests would exclude this disease. It is important to note that pulmonary tuberculosis is one of the most frequent intercurrent diseases encountered in chronic infantile beriberi.

*Syphilis* loss of weight, enlarged liver and eventually oedema may suggest congenital syphilis. The appearance of the oedema (which is slight and usually localized, e.g. in male infants only the scrotum may be affected), the absence of syphilitic eruptions and haematological examinations may exclude this infection.

*Czerny's "Mehlnahrshaden"* (carbohydrate intoxication) the condition described by Czerny is so similar to chronic infantile beriberi that, in all probability it is none other than chronic B avitaminosis.

As can be seen the term "infantile beriberi" is not synonymous with "beriberi in infants" as infantile beriberi is a separate entity which differs

considerably from the adult types of beriberi in its aetiology symptomatology and course

As already mentioned infantile beriberi may be easily overlooked when its presence is not suspected and its manifestations are not understood. Therefore it is comprehensible that even in the last *Annual Medical Report* (1939) infantile beriberi is not mentioned as a causative factor in infantile morbidity or mortality in Hongkong. Actually in the same report in a table entitled "Incidence of different types of beriberi with its bearing on age, no reference has been made to any cases under 6 years of age. It appears that the extremely high infantile mortality (345 per thousand live births) is attributed mainly according to pathological findings, to respiratory diseases such as bronchitis and bronchopneumonia and to enteritis.

However since 1940 infantile beriberi has been identified in one mortuary (conducted by the Hongkong University) to the extent of 53.3 per cent of all beriberi cases thus confirming the writer's statements published earlier that year (FEHLY 1940 and FEHLY 1941a).

Since infantile beriberi is caused by the ingestion of the milk of B<sub>1</sub> avitaminotic women one is inclined to ask what is the cause of such widespread maternal B<sub>1</sub> avitaminosis?

It is known that beriberi is endemic in all countries where white i.e. highly milled rice represents the staple food of the population. In South China rice is exclusively the staple food but fortunately as a rule people in villages and small communities consume unmilled or handpounded rice, highly milled rice being available in the larger communities only. Consequently beriberi may be regarded mainly as a disease of urban areas. In this connection Hongkong is most unfortunate because virtually all the rice required is imported largely from Siam and Indo-China. Partly owing to the preference of the population for white rice and partly on account of the better keeping qualities of such rice, practically all the rice imported by merchants is highly milled, the degree of quality referring mainly to the absence or presence of broken grains. After importation possibly in damp badly ventilated and insect infested ships, rice is stored for varying periods in godowns many of which also are damp, badly ventilated and insect infested. Thus white rice having been deprived of most of its vitamin B<sub>1</sub> by milling is subjected to a further reduction of its vitamin content through storage (insects, mould, etc.) washing and cooking. Consequently such rice when consumed has very little (if stored for short periods only) or no vitamin at all.

As already stated the requirements of vitamin B are in direct proportion to the amount of carbohydrates consumed. In case carbohydrates such as white rice are deprived of their vitamin, the required amount of vitamin B<sub>1</sub> should be derived from supplementary food. In South China such supplementary food consists mainly of vegetables and small quantities of fish. As vegetables (except some legumes) are only a fair source of vitamin B<sub>1</sub>, the



amount required is often beyond the physical and economic possibilities of the people. It is estimated that if one's diet consists of white rice and vegetables, there should be 2 catties (1 cattie = 1.33 lb) of vegetables for every cattie of rice consumed. In Hongkong Chinese males of the labouring classes may consume 1 to 2 catties and females  $\frac{1}{2}$  to 1 cattie of rice per day whilst the amount of vegetables rarely exceeds 1 cattie although it may be supplemented by small quantities of fish, some sauce and occasionally meat. As a result avitaminosis is widespread, causing not only beriberi but also lowered resistance against such infections as bronchopneumonia, tuberculosis, etc. Consequently amongst the people of South China, Hongkong has achieved a reputation for being unwholesome, but this is attributed to "bad water" and it was quite common for labourers, who are mostly immigrants to return to their native villages for cure as soon as they perceived the first symptoms of disease (mostly "weak legs," i.e., beriberi). As regards women probably due to the fact that they consume less rice and relatively more supplementary food the incidence of beriberi is not so high unless some additional burden is imposed on the female organism, e.g., pregnancy and lactation. In these conditions B avitaminosis is common and results in abortions, miscarriages, stillbirths or in infantile beriberi. In fact, due to B<sub>1</sub> avitaminosis paresis and paralysis during pregnancy and lactation are so frequent that these conditions are regarded by the Chinese in Hongkong as physiological effects of child bearing.

In addition the problem of B avitaminosis in Hongkong is aggravated by food customs and prejudices. One of the early symptoms of B avitaminosis is gaseous distension of the abdomen known as "*fung*". To the presence of this *fung* are attributed most of the symptoms of beriberi such as vomiting, chest oppression, palpitation, etc. whilst lactating women firmly believe that they transmit it, through the milk, to their infants (hence the name "*fung taam*" (wind-mucus) for acute infantile beriberi). An explanation was sought for the presence of *fung* and the erroneous conclusion was reached that it was caused through "cooling" food, which includes most fruit and vegetables. Whenever the symptoms of any disease begin to appear and invariably during the first month of lactation, "cooling" food is completely eliminated from the diet and the affected persons subsist on "hot" food, consisting of rice, a few bits of salted fish, a salted egg and, in the case of lactating women, ginger. In the case of male infants the mothers are especially "careful" and frequently abstain from "cooling" food during the whole period of lactation thus aggravating their condition and precipitating the appearance of the dreaded *fung taam* in their infants.

Although the preventive measures for B avitaminosis are not within the scope of this paper and have been commented upon by the writer elsewhere (FISHER 1941), it is interesting to note that the substitution of undermilled rice for the highly milled product in some neighbouring countries brought about the desired results. At the same time such undermilled rice contained approxi-

mately 25 per cent of external layers), in addition to being beriberi protective is the nearest approach to white rice as regards appearance taste and time required for cooking. Consequently it would seem that the substitution of undermilled rice for the highly milled product is the most suitable prophylactic measure to adopt.

## SUMMARY

1 The protean manifestations of infantile beriberi are discussed. It is suggested that their appearance and nature are determined by the localization and concentration of toxic metabolites.

2 The frequent appearance of secondary diseases mostly affecting the respiratory tract, is discussed. The oedematous condition of the respiratory organs is given as the probable main reason for such complications.

3 A number of diseases with similar symptoms are considered and the differential diagnosis discussed.

4 Some of the causes of widespread maternal B, avitaminosis and its effect on infantile mortality are mentioned.

## REFERENCES

- AALMEIER W. C. & WENGERACH H. F. (1928). *Herz und Kreislauf bei der Beriberi Krankheit*. Berlin: Urban und Schwarzenberg.
- ALBERT J. (1931). *Philipp J Sci* 45, 297.
- BARKIN B. P. (1933). *Canad med Ass J* 29, 5.
- FEHLY LYDIA (1940). *Caducus* 18, 76.
- (1941a). *J trop Med (Hyg)* 44, 21.
- (1941b). *Trans R. Soc trop Med. Hyg* 35, 177.
- (1941c). *Chinese med J* 60, 53.
- FISCHLER F. (1927). *Z phys Chem* 165, 53, 68.
- GUERRERO M. S. & QUINTOS. (1910). *Etiología del beriberi en los niños de pecho*. *Bull. Manila med Soc* 2, 243.
- HARIDAS G. (1937). *J Malay Br Brit med. Ass.* 1, 27.
- HIROTA, Z. (1891). *Z. med. Ges Tokyo*.
- ITO S. (1911). *Zuga Zanki* No 137.
- PLATT B. S. & LU G. D. (1939). *Biochem J* 33, 1525.
- SJOLLEMA, B. & SEEDLES L. (1926). *Biochem Z* 176, 431.
- SURE, B. KIK, M. C. & BUCHANAN K. S. (1935). *J Biol Chem* 108, 11.
- TAKAMATSU A. (1934). *Tohoku J exp Med.* 23, 46.
- WILLIAMS, R. R. & SPIES, T. D. (1939). *Vitamin B<sub>1</sub> (Thiamin) and its Use in Medicine*. New York: Macmillan.



# SOME OBSERVATIONS ON THE STUDY AND CONTROL OF YELLOW FEVER IN AFRICA WITH PARTICULAR REFERENCE TO THE ANGLO-EGYPTIAN SUDAN

BY

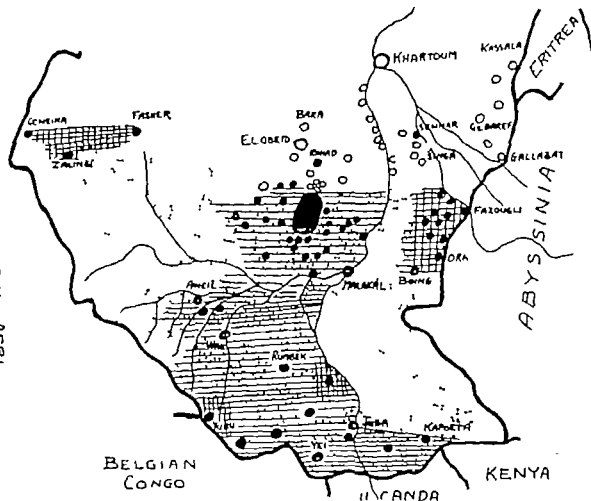
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## INTRODUCTION

The demonstration that yellow fever is transmitted by *Aedes aegypti* launched one of the most memorable campaigns in the history of preventive medicine. Its object was the complete eradication of yellow fever, first of all from the Americas, finally perhaps from the whole world. It was based on the belief that the virus of yellow fever was to be found only in man and in the *A. aegypti* mosquito. Since there are no human carriers and *A. aegypti* is incapable of transmitting the virus through the egg from one generation to the next it was held that the virus could not maintain its existence except in the presence of active *Aedes* having access to a continuous supply of non-immune human beings such as was to be found only in the great cities and such smaller places as had a constant supply of travellers from non-endemic areas. If by *Aedes* control the disease could be eradicated from such 'endemic seed beds' it might be expected to disappear also from the surrounding 'tributary areas'. In practice it seemed that the final proof of this argument was furnished by the results of GORGAS in Havana and Panama, since the sanitation of these two cities was followed by the disappearance of the disease not only from

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MAP I.—SHOWING THE KNOWN DISTRIBUTION OF YELLOW FEVER IMMUNITY IN THE ANGLO-EGYPTIAN SUDAN

This map should be read with the reservations indicated in the text. The area of immunity is shown stippled. Superimposed horizontal ruling indicates regions in which immunity has been found in children as well as in adults. Crossed horizontal and vertical ruling indicates regions in which immunity has been found in adults only. Simple stippling indicates unsurveyed regions. The actual places in which sera have been collected are also shown.

- Indicates places where immune donors were found
- Indicates places where no immune donors were found

The large black area indicates the position of the epidemic in 1940

Havana and Panama but also from many other cities of the Gulf of Mexico and the Caribbean Sea. Similar results followed the application of similar measures in other parts of the Americas. Only after 25 years had elapsed did it finally become evident that this sequence of events does not invariably occur.

The behaviour of yellow fever in Brazil during 1928 and 1929 revealed that although sanitation of all the larger cities and seaports of Brazil produced a striking reduction in the observed incidence of the disease, complete disappearance from tributary areas did not occur as it apparently had done in other parts of the Americas where similar measures had been undertaken. Meanwhile BAUER (1928) had shown that other mosquitoes besides *A. aegypti* can transmit yellow fever. The development of the mouse protection test, enabling the distribution of yellow fever immunity to be accurately mapped out by surveys, stimulated further studies from which it is now apparent that the epidemiology of yellow fever is more complex than was formerly believed. Summing up the position in South America, SOPER (1938) states that 'studies since 1930 have shown that there were two unknown epidemiological factors which doomed to failure the attempt to rid the continent of yellow fever by sanitation of the endemic seed-beds of infection viz (1) Rural yellow fever, transmitted by *A. aegypti*, and (2) jungle yellow fever occurring in the absence of *A. aegypti*. This last form occurs in rural and jungle areas, and at isolated points along certain river banks, where the population is low, and its movements so small that cases would seem to be accidents in an epizootic rather than parts of an epidemic.

There is growing evidence that the position in Africa is similar in many respects to that in South America. The essentially rural nature of the infection in Africa is becoming apparent in the distribution of yellow fever as revealed in protection-test surveys, but most of the African epidemics hitherto recorded have been of the classical 'urban' type. *A. aegypti* has generally been found when looked for and control measures undertaken along the traditional lines have apparently been successful although BRUWKEs *et al* (1933) suspected that *Taeniorhynchus africanus* might be an alternative vector in Kano.

During 1940 an extensive epidemic of rural yellow fever occurred in the Nuba Mountains district of the Anglo-Egyptian Sudan. Several different vectors were almost certainly concerned in the transmission (Lrwis, 1943), *A. aegypti* being probably of minor or no importance, since observations in the affected areas indicated a density of this mosquito which is generally considered sufficiently low to prevent the epidemic spread of *aegypti* transmitted yellow fever. It was realised that attention would have to be directed to other control methods than the reduction of *A. aegypti* and measures designed to limit the spread of the disease were devised in the light of (a) certain geographical, climatic and social conditions existing locally, and (b) recent work on the epidemiology of yellow fever including immunity surveys which had

previously been carried out locally in the affected districts. It is impossible to state whether the measures which were taken played any part in preventing the spread of the epidemic to adjacent territories. It is impossible even to estimate whether there would have been any likelihood of such a spread occurring if no measures had been taken at all.

While the occurrence of this epidemic in the Sudan has raised new problems connected with the future control of yellow fever in Africa, it did much to elucidate the epidemiological position. It clarified points on which there had previously been wide differences of opinion and to a large extent confirmed the results of previous investigations on yellow fever in Central and East Africa. The present communication is concerned primarily with the studies which have been carried out during recent years in the Anglo-Egyptian Sudan. Of necessity it includes frequent references to observations made in other countries, and to much that is already commonplace knowledge concerning yellow fever. It should be added that the writer is personally responsible for any opinions or suggestions put forward in this paper—they do not indicate the views or policy of any government or other institution.

## THE DISTRIBUTION OF YELLOW FEVER IN AFRICA.

### IMMUNITY SURVEYS.

Less than 25 years ago it was believed that the distribution of yellow fever in Africa was restricted to a narrow strip of territory on the West Coast.

The immunity survey of Africa, which was initiated some 10 years ago (SAWYER and WHITMAN 1906), produced the unexpected revelation that many of the inhabitants were immune to yellow fever in a broad band of territory extending across the continent from the West Coast as far eastwards as the river Nile. Although cases and epidemics of yellow fever had always been well known in the western portion of this region, there was at the time no satisfactory evidence that the disease had ever been present in the eastern portion, which included an extensive area in the Anglo-Egyptian Sudan. No epidemics had been reported among the native populations, and no Europeans stationed in places where a high proportion of the natives showed immunity had ever been known to contract the disease. Moreover a number of Europeans and natives whose blood was tested because they gave a history of an illness with signs and symptoms suggesting yellow fever showed no evidence of having developed immunity. The term *silent area* was commonly used to denote the region in which immunity was widely distributed, apparently in the absence of clinical cases. Although the findings gave rise to a good deal of speculation, the immunity surveys were continued and extended during the next 4 years, with the result that at the present time fortunately the distribution of yellow fever immunity in Africa is known with some degree of accuracy.

*Apparent Absence of Clinical Cases*—During the same period attempts were also made to identify clinical cases of yellow fever within the 'silent area' by (1) the examination of liver sections from fatal cases with signs and symptoms suggestive of yellow fever and (2) immunological tests in cases of obscure febrile conditions associated with jaundice.

An organised viscerotomy service of the type described by SOPER, RICKARD and CRAWFORD (1934) does not exist in the Sudan, and at the present time it would be quite impossible to establish it. Since 1933 however the main hospitals in the endemic area have been provided with viscerotomes, and medical officers were urged whenever possible to obtain liver sections either by viscerotomy or by autopsy from persons who had died after any obscure febrile illness of less than 10 days duration. Of sixty-five livers thus obtained during the period 1933-1939 all, save two were negative, and there were no undoubted positives. A doubtful case was reported by HEWER (1934) in a patient who died in Wau after an illness which resembled yellow fever clinically and in 1935 a specimen obtained from a Nuba who died in Malakal was considered suggestive of yellow fever. In neither instance were the sections typical. In the remaining negative cases the sections, although not suggestive of yellow fever, often showed acute and extensive hepatic necrosis.

Mouse protection tests with the sera of hospital patients suffering from obscure febrile conditions associated with jaundice failed likewise to reveal any cases of yellow fever infection (KIRK, 1936). It was noted, however that one of the writer's colleagues developed immunity after a short febrile illness contracted in the Nuba Mountains, but this illness was not observed by anyone other than the patient, and his description of it bore no resemblance to textbook yellow fever (cf. FINDLAY, KIRK and MACCALLUM, 1941).

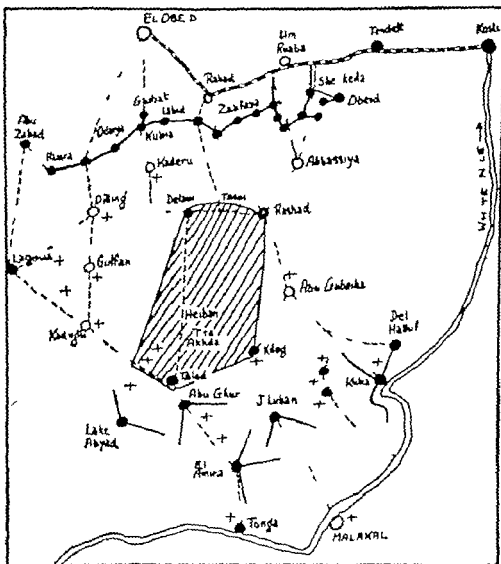
Until 1940 the results of the work may be summed up as follows —

(1) Numerous mouse protection tests indicated that yellow fever immunity was widely distributed in some areas of the Sudan as were also *A. aegypti* and other potential vectors of the virus, yet clinically recognizable cases of yellow fever could not be found.

(2) It had been demonstrated pathologically and immunologically that the cases of febrile jaundice which occur commonly throughout the Sudan, and which vary from mild clinical attacks to severe illnesses with deep jaundice, black vomit, and rapidly fatal outcome, are not due to yellow fever infection but to some other condition which may sometimes resemble yellow fever clinically but is apparently different from it aetiologicaly. The cause of the condition is entirely unknown, and attempts to elucidate it have so far been unsuccessful (KIRK, 1938). The information at present available does not even justify the assumption that all cases of this obscure jaundice syndrome have a common aetiology.

In view of those results it is not surprising that those who were, unac-





MAP 9.—SKETCH MAP OF THE NUBA MOUNTAINS AREA

The epidemic area (and inner control) is indicated by diagonal ruling in this area police posts and patrols are not shown in detail. Other symbols are as follows:—

————— Railway

----- Roads,

————— Police patrols

● Police (or quarantine) posts

+ Indicates places in which yellow fever immunity had previously been demonstrated

quainted with recent work in South America became sceptical about the significance of the immunity revealed by the mouse protection test, and a number of ingenious hypotheses were invented to explain the positive results.

#### DISTRIBUTION OF YELLOW FEVER.

The Nuba Mountains epidemic did much to remove scepticism, since it involved thousands of cases which were shown (KIRK 1941) clinically pathologically and immunologically to differ in no way from cases of yellow fever in other parts of the world. Strains of virus isolated during this epidemic and subsequently in Uganda (MAHAFFY *et al.*, 1941-1942) have not been found to differ in any essential features from yellow fever viruses isolated in West Africa and South America. It is now known that the distribution of yellow fever in Africa as determined by actual cases is practically co-extensive with the distribution of yellow fever immunity as determined by protection-test surveys, and involves an area in the central part of the continent covering approximately 4 000,000 square miles. This region is bounded on the north by a line which passes from St. Louis, Senegal through El Fasher to Dilling, then bends south of Rashad in the Nuba Mountains crosses the White Nile south of Jebelain and continues eastwards to the Abyssinian border on the west by the Atlantic ocean and on the south by a line passing due eastwards from a point on the Atlantic coast just south of Santo Antonio de Zaire. The eastern boundary has been accurately determined in Uganda (HUGHES JACOBS and BURKE, 1941). In the Sudan the area of immunity extends as far eastwards as the Abyssinian frontier, after which its limits have still to be determined. It may be noted, however that the immunity surveys published by FINDLAY, KIRK and MACCALLUM (1941) record no immune bodies in children from the area east of the White Nile. In view of this, the present writer carried out a further and more extensive survey of the Southern Fung area in 1942, but the results were consistent with those of the previous surveys. A high immunization rate among adults was found in many places, but protective sera were not obtained from children under 16 years of age although many donors were tested. The results suggest that the virus has not been active in this area during the last 16 years but the significance of this finding in relation to the present endemic distribution of yellow fever awaits further investigation. Map I shows a similar absence of protective sera from children under 16 years of age in the surveys of Geneina and Fasher on the extreme northern limit of the area of immunity, and in other places but in these instances the numbers of sera tested are too small to have much significance. This map should be read with some reservations. It does not pretend to show in accurate detail the distribution of yellow fever immunity throughout the Sudan but is merely an attempt to show graphically the results which have already been obtained. Much of the area

shown as unsurveyed is inaccessible or sparsely populated country. Immunity in adults but not in children is shown in certain areas where only a few sera have been collected, and it is possible that alterations will be required after further surveys. It will be noted that Sennar, Singa and Rahad, three places in which odd positive donors were found (cf. FINDLAY, KIRK and MACCALLUM, 1941) are placed outside the endemic area. This represents the writer's personal interpretation of the actual findings, based on the following considerations.

(1) The three places concerned are separated from the main area of immunity by a clear negative area. (2) They are populous centres on busy routes of travel, and before the recent intensification of anti-*aedes* measures there was no scarcity of mosquito vectors in them, so that if infection had been introduced into any of these three places in the past, one might reasonably expect to find a high proportion of immune donors instead of merely an occasional one. (3) The positive donors were in each case adults, and there was evidence to suggest that the immunizing infections might have been acquired during visits sometime in the past to places within the endemic area proper.

In the present state of knowledge, it is probably a wise precaution to regard the endemic yellow fever area in Africa as co-extensive with the area of immunity. Within the region thus defined conditions vary from place to place. The immunity rate is high in some places, low in others, and there are even places in which no immunes are found. Epidemics may occur but with the possible reservations indicated above the region as a whole may be regarded as endemic in the sense that the infection is always present and widely distributed.

Immunity surveys have been carried out in a number of other countries, and the world results, summarized by SAWYER (1935) indicate that there are two vast circumscribed endemic areas of yellow fever—one in Africa and the other in South America, outside which epidemics are very infrequent under present conditions. It is interesting to contrast the historical development of knowledge relating to yellow fever in the two continents. For various reasons, including the slave trade and the opening up of the New World to modern imperialism and commerce, yellow fever in the Americas was carried to many places outside the boundaries of its present distribution. During a campaign to eradicate yellow fever from the American continent recognition of the present endemic area began with the discovery that measures which had apparently been successful in other places failed to eradicate the infection from certain areas owing to the presence of hitherto unrecognized epidemiological factors. In Africa, on the other hand, the limits of the present endemic area were first defined by immunity surveys, which produced the unexpected revelation that the virus was widely distributed throughout a vast "silent area" in which there had not previously been any reason to believe that yellow fever existed. The discovery of clinical cases occurred subsequently and, as far as can be

ascertained there is no evidence that any extensive African epidemics of yellow fever have occurred far from the boundaries of the present endemic region.

### EPIDEMIOLOGY OF YELLOW FEVER IN AFRICA.

It is becoming increasingly evident that the subject of yellow fever in Africa is more complex than was at one time supposed. The factors responsible for the maintenance and propagation of the virus in the endemic region are still in large measure unknown but data accumulated during the studies we have mentioned, especially during the epidemic of 1940 call for some modification of previous views on the epidemiology of the disease. Much work has still to be done particularly on the subject of transmission, before any complete account of this can be written. In the present state of knowledge it is convenient for practical purposes to differentiate three epidemiological types of yellow fever in Africa (FINDLAY 1941). These are —

1 *Urban yellow fever* of the classical type occurring in towns and cities transmitted entirely or principally by *Aedes aegypti*. This is the type which has been so frequently observed in West Africa, of which the outbreak in Senegal described by FINDLAY and DAVEY (1936) may be taken as an example. According to those authors, yellow fever is not endemic in the town of Banjul but the virus is periodically re introduced probably from the surrounding country by means of an infected human being or animal, or by infected mosquitoes. In such instances there is no need to invoke factors other than (1) the virus (2) the non immune human being and (3) the vector usually *A. aegypti* to explain the subsequent course of events. Whether an epidemic actually occurs will depend on the proportion of non-immunes in the population and the *Aedes* index.

2 *Rural epidemic yellow fever* in which the disease assumes high proportions in a rural area where may be evidence of its previous existence. The vector may or may not be *A. aegypti*. The best example is the epidemic of 1940 *A. aegypti* although present in the affected area, was not the vector responsible for the epidemic spread of the disease. In this epidemic the principal vectors were *Aedes vittatus*, *Aedes taylori* and *Aedes fowleri* (FINDLAY 1943). Different vectors will probably be involved in rural epidemics in other places. It is also likely that various subsidiary vectors become involved in the height of a large rural epidemic, when large reserves of virus are present in the human population. Any species occurring locally which can transmit the virus and has access to infective cases, may become involved and contribute to spread the disease.

3 *Rural Endemic Yellow Fever* — In several places in Africa a high percentage of positive donors is found in immunity surveys. These immunities are distributed through all the age groups in the absence of any obvious epidemic.

of yellow fever. In certain places a much higher immunization rate for adults as compared with children has been recorded (HUGHES, JACOBS and BURKE, 1941). If the specificity of the mouse protection test be accepted it is difficult to explain such results otherwise than on the assumption that infection has occurred repeatedly in the same community without becoming epidemic. The fact that truly sporadic infections occur in Africa requires further proof but apparently isolated cases have been observed, as in Freetown in 1935 in the Belgian Congo in 1937 and 1940, and in the French Sudan in 1938 (FINDLAY 1941). Some of these cases have occurred in areas of low immunity but one of the writer's colleagues contracted an apparently sporadic infection during the rainy season of 1936 at Kau, in the Nuba Mountains. In this instance it had been found during the previous dry season (KIRK, 1936) that approximately 90 per cent. of the population at Kau were immune to yellow fever and it may be questioned how the virus was able to persist in a locality under such circumstances on the basis of a simple man-mosquito-man cycle. Unfortunately in none of the instances cited can it be stated categorically that no mild infections occurred among Africans in the vicinity at or near the same time.

*Origin and Effects of Epidemics*.—Such observations, and the results of the immunity survey of Africa, seem to indicate the existence in this continent of an endemic type of yellow fever comparable in many ways to the so-called jungle yellow fever of South America. The facts relating to its endemicity and method of transmission are unknown—they may be similar to those responsible for the maintenance and propagation of jungle yellow fever in South America, or they may be peculiar to Africa. Given the conditions which exist in many African towns, viz: a large non-immune population and many *A. aegypti*, it is easy to see how the accidental introduction of virus by an infected mosquito or an infected human being circulating virus in his blood might produce an urban epidemic. It is not so easy to understand why the disease should suddenly assume epidemic proportions in a rural area where there is evidence of its previous endemicity. Academically it may be questioned whether it is justifiable in the present state of knowledge to differentiate between epidemic and endemic types of rural infection in Africa, especially as SOPER (1937) suggests that the epidemiology of rural and jungle yellow fever in South America will be shown after further study to be the same, except where *aegypti*-transmitted infection is concerned. The present writer believes the distinction is useful in practice, for two reasons.

(1) In the first place, it seems that certain suitable conditions must arise before the disease assumes epidemic proportions in a rural area. The precise nature of these conditions is unknown, but records from the Nuba Mountains indicate that something more is required than the mere introduction of virus into a non-immune section of the population where vectors are present. Thus, in Moro, Tira Lunon, Heiban, and Tira Akhdar all districts which suffered heavily during the epidemic of 1940 there was evidence that the virus had

previously been among the populations to a varying degree (KIRK, 1941) yet suitable conditions for its epidemic propagation apparently did not arise until 1940.

(2) In the second place, during epidemics large reserves of virus accumulate which are highly explosive epidemiologically. When the disease assumes epidemic proportions in any locality within the endemic area, the tendency to infection (CURRIE, 1930) in that locality becomes temporarily greatly enhanced. An enormous increase in the number of infected mosquitoes occurs and the danger of infection spreading to adjacent territories becomes correspondingly greater. Thus a rural epidemic which took place in 1937 in the Gold Coast, in isolated villages in the Shai and Krobo districts to the north and north-east of Accra, was followed by a small explosive urban outbreak in Accra itself (FINDLAY 1941). More impressive examples can be cited from the experience of the New World. During the Rio de Janeiro epidemic of 1929 infection was carried along the American coast from points extending from Buenos Aires to Para, and up the Amazon to Manaus, a total distance of over 4 000 miles. The disease broke out in cities which until then were believed to have been rendered non infectible by *Aedes* control. According to SOPER (1938) the density of *aegypti* in these northern capitals was apparently sufficiently low to prevent the occasional case from the surrounding endemic areas giving rise to visible outbreaks of yellow fever but was not low enough to withstand the bombardment of virus from maritime contact with an infected coastline fed by the Rio epidemic. The presence of epidemics in any area may therefore have an important influence on the control of the disease in distant places. Their recognition and control even within the endemic area, may be an important factor in preventing the spread of yellow fever.

#### FACTORS INFLUENCING THE CONTROL OF YELLOW FEVER.

The control of yellow fever includes (1) the elimination of the disease from a community in which it exists in epidemic form, and (2) prevention of the spread of yellow fever to parts of the world at present free from it.

The same methods are available for both purposes, but the machinery required for their application may be very different. Where the elimination of epidemic yellow fever from an infected community is concerned the result can be achieved by local action only and it is probably safe to say that the whole-hearted co-operation of the community will generally be available, even in support of the most rigorous and arbitrary measures which it may be considered necessary to adopt.

Prevention of the spread of yellow fever is a very different matter. It requires all the complicated machinery of co-operation between governments. It may call for large expenditures of money or the imposition of restrictions which adversely affect trade and prosperity even when no danger is apparent.

to the lay members of the community. Also it requires more knowledge than we have at present on the one hand to determine accurately the existing dangers and the precautionary measures required to meet them, on the other hand to minimize the possibility of commerce being dislocated by ill-designed measures to prevent calamities that will never occur. The principles of prevention are simple. They are first, preventing the transfer of virus from the endemic regions to places outside them at present the only two factors by which the possible transfer of virus is considered at all likely are infected mosquitoes and infected human beings. The second principle of prevention is to render places non-infectible so that if the virus is accidentally introduced it will be unable to survive, and will rapidly die out. It used to be thought that the absence of either *A. aegypti* or susceptible human beings would suffice to make a place "non-infectible." Probably this is so in the case of cities, and at the present time we have the means at our disposal to produce both desiderata very rapidly. In the case of rural areas the position may be different this is one of the points on which further knowledge is required.

#### METHODS.

The Nairobi Conference on yellow fever grouped control measures under three headings:—

- (1) Mosquito control.
- (2) Quarantine.
- (3) Inoculation.

FINDLAY (1941) stresses, in addition, the importance of early diagnosis in the control of yellow fever. In the event of cases occurring outside the endemic area, or of the disease suddenly assuming epidemic form in the endemic area near its borders, accurate and early diagnosis is obviously a matter of supreme importance. It is of less importance, and as a rule impracticable, in the case of sporadic infections or small outbreaks occurring in remote and inaccessible places within the endemic area.

SOPER (1938) dealing principally with the endemic area in South America, emphasizes that viscerotomy should be regarded as a basic part of yellow fever control. By viscerotomy SOPER means not merely the examination of liver sections to confirm diagnosis in suspected clinical cases, but the organization of an extensive supervised collecting service, in which appointed non-medical representatives with legal sanction obtain specimens of liver tissue from all persons who have died after a febrile illness of less than 10 days duration.

#### *Urban Yellow Fever*

The relative importance of each of the above methods in any control scheme will vary in different circumstances, and more especially with different epidemics—

logical types of yellow fever. In urban yellow fever—the classical yellow fever of history on which CARTER (1931) based his lucid exposition of the epidemiology of the disease—three factors only need be considered: the virus, the non-immune human being and the vector, usually *A. aegypti*. In practice this means that three things—(1) cases of yellow fever, (2) susceptible human beings and (3) active *Aedes* having access to both (1) and (2)—are necessary and sufficient for the continuance of the disease. A break in this chain, even for a short time, will end the occurrence of fresh cases. Complete control of any one of the three factors will suffice. The epidemic may be brought to a close by either (1) failure of the human host through immunization of susceptibles, or (2) elimination of the insect vector.

The writer has no experience of urban yellow fever, but the experience accumulated during the past 40 years by some of the world's most illustrious sanitarians indicates that it should generally be possible to control urban epidemics by measures directed to the elimination of *A. aegypti*, although in specialized circumstances the control of certain other species prevalent locally might have to be included where these tend to replace *A. aegypti* in importance, e.g. *Taeniorhynchus africanus* in Kano (BEEUWES *et al.*, 1933) or *Aedes pembaenensis* in Mombasa (LISTON 1941). A matter urgently requiring further study in connection with the possible spread of yellow fever is the prevalence and importance of vectors other than *A. aegypti* in the large cities and seaports into which it is considered possible that the virus may be introduced.

### Rural Yellow Fever

The remarkable success which has been achieved in the control of urban yellow fever in the New World is primarily dependent on the fact that the species sanitation of *A. aegypti* can be made remarkably efficient. Unfortunately, the same methods are generally inadequate to meet the case of rural yellow fever where other vectors are frequently involved. Only in one instance have they been successfully employed. SOPER (1938) describes how the problem of rural yellow fever in north-east Brazil was solved by the extension of the anti-*aegypti* service to rural areas. The results were similar to those obtained in towns and cities. Yellow fever was rapidly and completely eradicated from a region comprising six States and a population of several million people. As far as the writer is aware, this is the only region in which true *aegypti*-transmitted rural yellow fever has been observed. The circumstances in which it occurred were somewhat specialized, owing to the nomadic habits of the people and semi-desert climatic conditions necessitating storage and transport of water by travellers, thus greatly facilitating the spread of *A. aegypti* in rural areas. The complete disappearance of the disease from the whole region following the extension of anti-*aegypti* measures to rural areas indicated that the persistence



of the infection in this region was entirely dependent on the association of man and *A. aegypti*.

Where vectors other than *A. aegypti* are concerned the control of rural yellow fever becomes complicated by several factors. Referring again to South America SOPER (1938) describes the control of yellow fever in Brazil as based wholly on viscerotomy anti-*aegypti* measures, and vaccination any discussion of auxiliary measures of control, such as quarantine, fumigation, isolation of cases or contacts in screened wards, is deliberately omitted, as SOPER considers that such methods are not suitable for control in endemic areas, although he admits their possible usefulness as emergency measures in non endemic areas. The control of yellow fever in Brazil, based on the three methods mentioned, has now reached such a satisfactory state that the epidemiological picture is now dominated by jungle yellow fever. Other types have been reduced to negligible proportions, and in the few minor *aegypti* transmitted outbreaks which have occurred in recent years investigations have failed to reveal any evidence of previous *aegypti* transmitted disease as a source of infection, but have suggested that the outbreaks originated from the importation of virus from the surrounding jungle. The control of jungle or endemic yellow fever does not at present envisage attempts to eradicate the infection from the endemic regions, since the means by which it is perpetuated are unknown. Control implies simply the protection of individuals by vaccination, prevention of the spread of infection to places outside the endemic regions, and the elimination of epidemics within the endemic region wherever this can be done.

### *Decline of Epidemics*

It has long been known that epidemics may die out spontaneously owing to immunization of susceptibles—the so-called failure of the human host. The course of a yellow fever epidemic in a community depends on quantitative relation between the proportion of susceptibles and the number of mosquito vectors. The "critical number" of vectors (CARTER, 1922) that is the minimum number required to maintain the infection, varies in different places, and at different times in the same place, according to many interrelated factors such as the size of the community the percentage of susceptibles, immigration of non-immunes, and bombardment by virus in infective cases from without. As the proportion of immunes in the population rises during an epidemic a greater density of the vector becomes necessary to keep the infection going, since the number of times a mosquito feeds during its lifetime is limited, and an increasing number of the infective bites will be wasted on immune individuals. A state of affairs may finally be reached, without any control measures having been undertaken, in which the epidemic will die out spontaneously even although vectors are still present and there are still susceptible human beings

in the community. It is probable that many historical epidemics of yellow fever ended spontaneously in this way.

In like manner a reduction in the number of mosquitoes as a result of sanitation which fails to attain complete eradication of the vector may suffice to stop an epidemic in its later stages although it would have been ineffective earlier. As a result of mass immunization the elimination of yellow fever from an infected community becomes easier in the later stages of an epidemic than at its beginning. Conversely, a very small number of vectors may suffice to produce an epidemic if the virus is accidentally introduced into an entirely non immune community.

With the discovery of an efficient vaccine it is now possible to produce mass immunity rapidly and safely by artificial means. Mass vaccination may be used to diminish the chances of an epidemic resulting from the accidental introduction of virus into a populous community where the vector may be present in small numbers. It has been extensively carried out in some of the cities and seaports of East Africa with this object in view. In certain circumstances mass vaccination may also be a valuable adjunct to mosquito control for bringing epidemics to a close. At the end of the Nuba Mountains epidemic it was so employed, to eliminate an apparently residual and circumscribed focus of the disease (see below). The procedure was sound in principle although its application in this particular instance was later shown to have been erroneous.

It has been said that the control of the insect vector is the sanitarian's method of ending yellow fever epidemics, whereas failure of the human host is nature's method. Even in nature however both methods may come into operation as we have described elsewhere (KIRK 1941) in the case of the Nuba Mountains epidemic. Immunization of susceptibles was possibly an important factor in certain places where an early decline of the epidemic occurred while it was still spreading in other places and while mosquitoes were still plentiful but the final close of the epidemic throughout the whole area was brought about by the seasonal elimination of mosquitoes following the onset of dry weather conditions.

#### EXPERIENCES IN THE NUBA MOUNTAINS

The Nuba Mountains outbreak was the first extensive rural epidemic in Central or East Africa for which preventive measures had to be instituted. It may be described as an emergency occurring within but on the borders of the endemic region. Vaccine was not immediately available and the preventive measures instituted were entirely dependent on sanitary isolation, or quarantine one of the auxiliary methods of control which have been discarded by modern workers in South America as unsuitable in endemic areas. Even the older authors do not write hopefully on the subject of quarantine. Thus CARTER (1922) states that maritime quarantine against yellow fever can be conducted

so as to be efficient with little interference with commerce. Of land quarantine the reverse is true, and if to be continued long it will fail practically always someone passing it in the period of incubation. However certain climatic features of the Nuba Mountains, which are described below suggested that prolonged quarantine might not be required, while the impassable condition of the country resulting from the rains would greatly assist the authorities in their attempts to secure absolute sanitary isolation of the Nuba Mountains from the rest of the country—for a time at least, probably until vaccine became available, or until the future behaviour of the epidemic could be determined.

The two objects of yellow fever control, as indicated in a previous section of this paper were clearly differentiated at the outset. It was decided that for the time being no attempt should be made to eliminate the disease from the affected area, or even to reduce its incidence, but that all the resources available should be mobilized in the attempt to secure complete sanitary isolation of the infected area, with a view to preventing the spread of the epidemic to places outside no matter what happened within the affected area. Particularly it was important that infection should not reach either the river or the railway line, whence its further spread might have been very rapid and disconcerting. This policy was adopted for a number of reasons which were peculiar to the circumstances in which this particular epidemic occurred viz —

- 1 Even inside the Sudan the risks at stake appeared considerable. The introduction of yellow fever among the Allied Forces operating at the time on the eastern frontier might have produced very serious consequences. The resources and staff available to prevent this were too meagre to risk any dissipation of them in attempts to control the disease inside the affected area.

- 2 The vector was unknown. *Aedes aegypti* was present in the affected area, but at an early stage it was suspected that this mosquito was of minor importance only and that other vectors were concerned.

- 3 Throughout the Nuba Mountains the end of the rains in October is followed by a rapid denudation of the country as a result of which mosquitoes disappear almost completely. The notable exception to this rule is *A. aegypti* owing to its domestic breeding habits in water stored in houses during the period of drought (Kirk, 1941). There was reason to believe that the march of the seasons would shortly eliminate vectors other than *A. aegypti* more rapidly and effectively than could be accomplished by control measures, so it seemed advisable to wait till the drying up of the country had occurred before any attempts at mosquito control were undertaken in the affected area. In the meantime arrangements were made to obtain as accurate records as possible of the distribution, extent, and movements of the epidemic by sending out hospital orderlies and native dressers to tour the villages of the affected hills, and record weekly the number of new and recovered cases and the number of deaths. It was considered that if their reports indicated the persistence of the disease in any localities after the general denudation of the country had eliminated

mosquitoes other than *A. aegypti* this would probably be the result of *aegypti*-transmitted infection in the foci concerned which could then be dealt with by methods of *aegypti* control in the usual way. It was estimated that a period of 4 to 6 weeks would suffice to clarify the position.

While these plans were being discussed attention was attracted to the fact that unusually large numbers of jaundiced patients were being observed in the out-patient department of El Obeid hospital. Clinical investigation suggested that these were cases of infective hepatitis which for some reason has always been prevalent in El Obeid but the possibility of yellow fever had to be considered, since, although El Obeid is separated by more than 100 miles from the area affected by the epidemic it has an important aerodrome besides being a terminus of the Sudan Railways. The population of El Obeid was known to be entirely non immune to yellow fever so use was made of CARTER'S (1922) extrinsic incubation period to exclude yellow fever on epidemiological grounds. House to house inspections were made and every sick person in El Obeid visited over a period of 14 days during which a strict quarantine system was enforced. The absence of any marked increase in the incidence of sickness during this period was against the diagnosis of yellow fever and the quarantine was modified accordingly. Laboratory investigations (FINDLAY, KIRK and LEWIS 1941) later demonstrated conclusively that there had been no yellow fever in El Obeid.

*Quarantine Measures*—The measures taken to prevent the spread of the disease have already been reported by CROUCH (1940) and need only be summarized here. They were designed to secure complete stoppage of all movement into and out of the Nuba Mountains area.

Cordons and quarantines were established round the area known to be infected (inner control) but in order that the main system of defence should be well outside any possible seat of infection an outer circle of control was designed to secure complete sanitary isolation of the whole Nuba Mountains area from the rest of the country. Police posts and patrols were established at selected points to prevent all movement to the railway the river and the west. The points were selected so as to control all portals of exit from the Nuba Mountains. Roads which had been closed by the rains were not re-opened. Air traffic to and from the area was prohibited aerodromes had likewise been closed during the rains and were not re-opened.

A quarantine was established 10 miles south of El Obeid to allow the passage of essential staff and supplies to and from the area. This was the sole route of entrance and exit. The period of quarantine was 10 days.

Supplementary measures were taken outside the affected area. Railways traffic was prohibited between El Obeid and Kosti and road traffic between El Obeid and Darfur and between El Obeid and Tendelti. Cross-river traffic was prohibited, and the embarkation and disembarkation of steamer passengers

between Kosti and Lake No. El Obeid aerodrome was made and declared anti amaril.

No case was known to occur outside the declared infected area. Except for continued reports of cases from Tagot (see below) the epidemic declined rapidly as the country dried up and finally came to an end according to the forecast. As we have stated it is impossible to estimate whether the measures instituted were in any way responsible for limiting the spread of the infection. Modern workers in South America do not regard quarantine as a method of control suited to endemic areas. Lest the history of this epidemic should create an unduly favourable impression of quarantine, it is necessary to emphasize that the epidemic occurred in somewhat specialized circumstances, which were peculiarly suited to this method of control, and may not be encountered in other epidemics. Two factors require special mention.

1 In the first place the epidemic occurred in a region in which the rains are restricted to one period of a few months every year alternating with a period of drought and desiccation. During the rains mosquitoes are abundant, and conditions are favourable for the transmission of mosquito-borne disease, but the country generally is impassable and movement is practically at a standstill. By the time the country dries up sufficiently to re-open communications mosquitoes have very largely disappeared, so that when movement is resumed on any appreciable scale conditions have become unsuitable for the spread of mosquito-borne disease. These circumstances greatly facilitated control in the three ways. In the first place the volume of movement during the epidemic was necessarily small, slow, restricted to a few well-known routes, and therefore easily controlled. Secondly a rapid and significant decline of the epidemic was evident before it became necessary to devise means of restricting any large volume of traffic for an indefinite period. Finally the re-opening of communication in normal years accelerated by various government activities such as the repairing and re-opening of roads, the removal of vegetation, draining of residual swamps and so on, so that by merely holding up those activities it was possible to delay the resumption of traffic very considerably without throwing any extra strain on the available staff.

2. The epidemic was one of major proportions, and produced considerable anxiety among the population. By the time quarantine measures were instituted the people were thoroughly alarmed and willing to co-operate actively in any measures designed to prevent the spread of the disease. It is the writer's belief that at the most critical period, when communications were beginning to re-open, and while mosquitoes were in the process of disappearing but occasional adults might still be found, the quarantine system was practically 100 per cent efficient, and that this was due to the co-operation of the people themselves more than to any other factors. No attempts were made to evade the quarantine stations no coercive measures were ever required at the police

posts or by the patrols to stop or detain intending travellers. A simple explanation that the way was closed 'because of the disease' immediately won their approval and willing compliance with whatever was necessary. The results could not have been obtained without the co-operation of the people, as was evident later when, after the epidemic had died out, restrictions were still maintained because of reported cases occurring in an isolated focus at Tagoi. The people, no longer convinced of the menace of the disease, now found the restrictions irksome. Complaints were numerous, the quarantine posts were evaded, and there is little doubt that at this period the quarantine system was by no means 100 per cent. efficient.

### *Vaccination*

When the first batches of vaccine were received priority in immunization was given first, to those at risk in the affected area engaged on work connected with the epidemic, and secondly to transport workers, so that essential services should not be hampered by the exigencies of quarantine. Owing to the presence of the Rockefeller Foundation, however, vaccine soon became available in ample quantities to provide for immunization on a much wider scale. The fact that vaccine was available on the scale required did much to relieve anxiety. This was a great boon, especially to those responsible for instituting measures to prevent the spread of the disease, since it enabled them to do so without creating undue alarm at a time of stress and emergency in East Africa. Also by the employment of vaccinated personnel, it was possible to maintain essential services to the affected area, thus reducing to a minimum the economic dislocation caused by a rigid system of quarantine.

### *Apparent Residual Focus of Aegypti transmitted Infection*

With the desiccation of the country and consequent disappearance of mosquitoes the epidemic had almost ceased by the beginning of December 1940 but it was reported that cases were still occurring in the Tagoi hilla, an isolated range some 10 miles west of Rashad. An entomological assistant was sent to investigate the mosquito situation in Tagoi. He reported that *Aedes aegypti* was abundant, the only mosquito present and that it was breeding in large numbers inside houses, the *Aedes* house larval index being as high as 98 per cent in some of the villages. In one village which had a lower index it was noted that the only section of the village affected by the disease was the only section infested by *A. aegypti*. In fact, Tagoi had every appearance of being one of the residual foci of *aegypti* transmitted infection which had been anticipated (see above) so it was arranged to open an intensive anti-*aegypti* campaign there, and to carry out mass vaccination of the population (approximately 1,500 people) so as to bring the whole epidemic rapidly to an end. At the same time it was resolved to attempt the isolation of virus from mosquito vectors

suggested is discussed in more detail by LEWIS (1943a) in connection with the distribution of mosquito vectors.

Occasional donors with protective sera have been found outside the endemic area in the course of immunity surveys. These are sometimes disconcerting, and apt to cause confusion in the construction of maps showing the distribution of yellow fever immunity. SAWYER and WHITMAN (1936) state that the chances of finding an isolated individual with protective blood seem to rise with the number of bloods collected and the nearness to the area of immunity. As possible explanations of such anomalous positives they suggest (1) infection of the donor with yellow fever virus when contrary to the information given, he had previously visited some distant place, (2) sporadic infections with the virus introduced into the locality or persisting there under conditions unfavourable to the spread of the infection, or (3) an exceptional concentration of some non-specific factor in the blood. At present it is impossible to say which of the three explanations is the more generally applicable, but until the second possibility can be definitely excluded such anomalous positives may well deserve further study. There is no justification for assuming that the introduction of an occasional case, even into places where non immune human beings and vectors are both present, will invariably produce an epidemic. The results in such circumstances are determined by the normal laws of mathematical probability operating on the factors which govern the propagation of yellow fever infection. SORRE's explanation of events in the northern cities of Brazil at the time of the Rio epidemic of 1929 (quoted above) emphasizes the importance of "virus bombardment" as a quantitative factor influencing the results which may be expected to follow the introduction of the virus into places where conditions do not particularly favour transmission. That certain communities need constant and rather heavy virus bombardment to maintain the infection is indicated by the disappearance of yellow fever from most of the towns and cities of the Caribbean region after the elimination of the disease from Havana and Panama.

#### COMMENTS.

It is exceedingly difficult to account for the distribution and persistence of yellow fever infection in some tropical regions in view of its absence, easy control, or spontaneous disappearance (CARTER, 1917) in others. Differences in meteorological conditions or density of population do not appear to be adequate explanations in all cases nor does the geographical distribution of *A. aegypti* while in Africa at any rate public health measures have played little or no part in confining the disease to its present distribution. All that can be said at present is that some conditions which favour the persistence of yellow fever in certain parts of South America and Africa apparently do not exist in other regions, such as those around the Caribbean Sea and the Gulf of Mexico.

where the disease can be easily controlled or has disappeared spontaneously. Further elucidation of the factors concerned is more than a matter of academic interest. At present it is uncertain whether conditions favouring endemicity exist in other parts of the world, which have been free from yellow fever so far, but into which the infection may spread yet the results of any proposed control measures might be profoundly affected by this consideration.

Among the possible factors which have been considered is the geographical distribution of vectors other than *A. aegypti*. It is now known that over forty different species can transmit the virus in the laboratory and there is evidence that vectors other than *A. aegypti* play an important part in the natural transmission of the disease in certain places. SOPER (1935) suggests that the discovery of vectors either having a longer life than the aedine mosquitoes, or being able to transmit the virus hereditarily would help to elucidate a number of points in the epidemiology of yellow fever but vectors fulfilling these requirements have not yet been found.

The discovery that yellow fever can persist in regions with few inhabitants and little travel has stimulated the search for alternative hosts to man, and it has now been found that 20 to 25 per cent. of wild monkeys in the endemic yellow fever areas of both Africa and South America have immune bodies in their blood. There is thus some indication that warm blooded animals such as monkeys might be able to maintain the virus in the absence of man, although SOPER (1937) points out that the infections responsible for the immunity in these animals may be accidents in the course of some other cycle of infection just as human cases seem to be. BUGHER *et al* (1941) believe that opossums like monkeys, may become naturally infected in South America. Protective substances have been found in the sera of domestic animals from the Nuba Mountains (FINDLAY *et al* 1941) and other places, but their significance is at present uncertain.

It is obvious that there are still big gaps in our knowledge of the epidemiology of yellow fever in Africa. Nevertheless, a number of important points have been elucidated in the last few years. Some years ago SAWYER and WHITMAN (1936) discussing the unexpected results of the first immunity survey in Central and East Africa, stated that persistent studies to elucidate (1) the symptomatology and pathology of the disease produced by the immunizing infections (2) the characteristics of the prevailing strain of yellow fever virus (3) the identities and habits of the blood-sucking anthropod vectors and (4) the presence or absence of warm-blooded hosts other than man, should make it possible to estimate the danger of yellow fever spreading to the eastern coast and help to determine the precautionary measures required. The main problems connected with the first two lines of enquiry indicated above have now been elucidated. From the preventive points of view this in itself is an important advance since the authorities concerned now realize that yellow fever



in Africa is not restricted to the West Coast, and are consequently in a better position to determine where preventive measures can be most effectively applied.

It is not the purpose of this paper to point out the danger of the spread of yellow fever. Nor does it purport to estimate the likelihood of spread occurring, or to indicate measures which might be taken at different places to prevent it. More knowledge is required before this can be done, but it is not easy to foresee the type of knowledge which is likely to be of most value in any circumstances of emergency. In the Nuba Mountains, for example, accurate knowledge of local communications and of local geographical climatic and social conditions was probably more useful than detailed information on the bionomics of all the possible vectors in the area would have been had this been available. The experiences we have described in the Sudan illustrate how difficult it may be even to obtain accurate information about the infections which must always be occurring at some point or other within the endemic regions. The virus may be present in places where there is no evidence of active disease, and where practically the whole population is known to be immune, as was instanced by the sporadic European infection at Kau in 1936. For this reason it is a wise precaution, in the present state of knowledge to regard the entire endemic region in Africa as potentially infective for purposes of quarantine regulations.

If in spite of all precautions, yellow fever should spread into some new territory the results cannot be predicted. But, as the disasters of the past were due to urban yellow fever so the prevention of future disasters will consist primarily in the prevention and control of urban epidemics. The discovery of new epidemiological factors, such as rural and jungle types of infection does not very much alter this conclusion. At the same time, the prevention of urban epidemics, especially in the great cities on the main highways of world communications, is the most important single measure for reducing the possibilities of the international spread of yellow fever.

In the event of spread occurring under abnormal conditions, as, for example, in time of war especially during active military operations, when routine mosquito control and other sanitary activities are disorganized, the consequences might be terrible. Apart from such conditions, however it has to be borne in mind that the control of yellow fever is now a very different matter from what it was in the old days of disastrous epidemics. Sanitarians in the New World, where most experience has been gained, hold that the time has now come when the occurrence of *egypti*-transmitted urban infection should be regarded as a serious reflection on the competence of the health authorities concerned. Thus SOPER (1935) states that "the protection of urban populations against yellow fever is today a problem of administration only. The technique is known and the results are sure. Such great progress has been made in reducing the cost of anti-larval work in recent years that urban

yellow fever can no longer be considered a public health problem, but rather an administrative crime.

Of rural infection this cannot yet be said. Within the endemic area rural yellow fever may be a serious public health problem in itself as was instanced by the magnitude of the Nuba Mountains epidemic. In addition it entails the possibility of the disease occurring unrecognized in remote localities whence under modern conditions its rapid and unsuspected transport to some populous centre where the *aegypti* density is high might lead to serious mischief. There is another possibility which though it may appear hypothetical cannot be excluded as long as the factors remain unknown which have hitherto served to confine the infection within its present distribution in Africa. This is that the spread of yellow fever might occur by a gradual extension of the present endemic area, in the absence, to begin with, of any noticeable epidemics or recognized cases. For this reason it is desirable that the boundaries of the present endemic region should be accurately delimited so that subsequent changes can be recognized if they occur.

## REFERENCES

- BAUER, J. H. (1928) *Amer. J. trop. Med.* 8 261.  
 BERUWKE, H., KERR, J. A., WETHERSREE, A. A. & TAYLOR, A. W. (1933) *Trans. R. Soc. trop. Med. Hyg.* 28 425.  
 BOVILL, E. W. (1933) *Caravans of the Old Sahara*. Oxford University Press.  
 BUGHIER, J. C., BOSHELL MAURIQUE, J., ROCHA GARCIA, M. & GILMORE, R. V. (1941) *Amer. J. trop. Med.* 21 309.  
 CARTER, H. R. (1917) *Trans. R. Soc. trop. Med. Hyg.* 10 119.  
 — (1922) Yellow Fever. In BYAM and ARCHIBALD's *Practice of Medicine in the Tropics* vol. 2. London: Henry Frowde and Hodder & Stoughton.  
 — (1931) *Yellow Fever: An epidemiological and historical study of its Place of Origin*. Baltimore: Williams & Wilkins Co.  
 CROUCH, H. A. (1930) *Proceedings Nairobi Conference Yellow Fever*.  
 CURRIE, J. R. (1930) *Textbook of Hygiene* p. 360. Edinburgh: E. & S. Livingstone.  
 EDWARDS, F. W. (1941) *Mosquitoes of the Ethiopian Region. III Culicine adults and pupae*. London: British Museum (Natural History).  
 FINDLAY, G. M. (1941) *Trans. R. Soc. trop. Med. Hyg.* 35 51.  
 — (1941a) *Ann. trop. Med. Parasit.* 35 59.  
 — & DAVEY, T. H. (1936) *Trans. R. Soc. trop. Med. Hyg.* 30 151.  
 — KIRK, R. & MACCALLUM, F. O. (1941) *Ann. trop. Med. Parasit.* 35 121.  
 — & LEWIS, D. J. (1941) *Ibid.* 35 149.  
 HEWES, T. F. (1934) *Lancet* 2 496.  
 HUGHES, T. P., JACOBS, H. R., BURKE, A. W. (1941) *Trans. R. Soc. trop. Med. Hyg.* 35 131.  
 KIRK, R. (1936) *Bull. Off. int. Hyg. publ.* 23 2340.  
 — (1938) *Trans. R. Soc. trop. Med. Hyg.* 31 667.  
 — (1939) *Ann. trop. Med. Parasit.* 33, 125.  
 — (1941) *Ibid.* 35 67.  
 LEWIS, D. J. (1943) *Ibid.* 37 65.  
 — (1943a) *Bull. ent. Res.* In the press.  
 — HUGHES, T. P. & MAHAFFY, A. F. (1942) *Ann. trop. Med. Parasit.* 36 34.  
 LISTON, J. M. (1941) *MIS Report to D.M.S. Kenya*.

- MARAFY A F HUGHES, T P SMITHURST K. C & HILL, R. (1911). *Ann. trop. Med. Parasit.* 28 141
- SMITHURST K. C., JACOB H. R. & GILLET J D (1912) *Trans. R. Soc. trop. Med. Hyg.* 26 9
- MANSION, P (1903) *Trans. epidem. Soc. Lond.* 22 60
- SAWYER, A W & WHITMAN L (1936). *Trans. R. Soc. trop. Med. Hyg.* 29 367
- SOPER, F L (1935). *Rural and Jungle Yellow Fever a New Public Health Problem in Colombia*. Bogotá Editorial Minerva S.A
- (1937) *Amer. J. trop. Med.* 17 655
- (1936) *Trans. R. Soc. trop. Med. Hyg.* 22 297
- RICKARD E. R & CRAWFORD P J (1934) *Amer. J. Hyg.* 19 549
- TOUSSAINT PRINCE OMAR. (1933) *Bravery of the Egyptian Sudanese Battalion in the African War In Arabi*. Published privately in Egypt
- WATSON M (1941) *Practitioner* 146 353

## HAEMOGLOBINURIA FOLLOWING THE ADMINISTRATION OF PLASMOQUINE

BY

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This case of severe haemoglobinuria following the administration of plasmoquine is recorded because the survival of the patient allowed certain observations to be made upon the mechanism of the toxic action of the drug. During the course of his illness, haemagglutinins were demonstrated in the patient's serum and it was possible to observe something of the renal damage which occurred.

### Case Report

The patient, a private soldier aged about 19 years and a native of Nyasaland was embarked in one of H.M. Hospital Ships on the 10th day of an attack of sub-tertian malaria. He gave no history of previous attacks nor of any serious illness and there was no record, at any time while he was under treatment, of splenic enlargement. The course of his illness up to the time of embarkation was in no way unusual. The onset was a sudden one with headache, backache, fever and a rigor. Gametocytes of *Plasmodium falciparum* were found in blood smears. He had been treated with quinine sulphate by mouth 30 grains *per diem* for 3 days. On the 4th day atabrin was given and continued for 5 days, the dose being 0.1 gramme t.d.s. He had no high fever after the 4th day.

When seen on the day of embarkation he appeared very well. There was no enlargement of the spleen and his urine was normal. After 3 clear days had elapsed following the cessation of treatment with atabrin he was given plasmoquine, 0.01 gramme t.d.s. and at the same time he received an alkaline mixture and extra fluids. Nothing of note occurred while he was taking plasmoquine except that he was given the drug for 4 days instead of for 3, the last dose being taken on 18th September. Three days later his temperature rose to 100° and in the evening he vomited, but he did not otherwise complain and no special observations were made. The following morning his temperature had fallen to 99°, his pulse rate was 116 while his respiratory rate was a little increased. The mucous membranes and the palms of his hands were

remarkably pale the liver and the spleen were not palpable. The urine was of a dark chocolate brown colour alkaline and with a specific gravity of 1018. Albumin was present in considerable quantity and the guaiac test was strongly positive. Bile salts, bile pigments and sugar were absent. On microscopical examination large numbers of epithelial cells were seen together with a few red cells but there were no casts.

The next day his condition was much the same that is, he felt well and apart from tachycardia, slight fever and obvious anaemia there was nothing to observe at the bedside. There was no demonstrable oedema. Examination of the blood revealed profound anaemia, the findings, together with those of the urine, being as follows —

1942 23rd Sept

*Blood Count*

Haemoglobin 30 per cent red cells 1.64 million per c. mm colour index 0.87

White cells 16,500 per c. mm

Blood group O the separated serum has a slight chocolate tint

*Urine*

Dark chocolate colour acid, specific gravity 1018

Albumin ++ guaiac test for blood + +

No bile salts, bile pigments or sugar detected

*Microscopical examination*

Very large numbers of epithelial casts present along with a fair number of red cells. A small number of hyaline casts and a few granular casts are also present.

Transfusion was decided upon. On cross-grouping however it was found that the patient's serum produced some, but not complete, delayed agglutination of the donor's red cells. The group of the donor was confirmed with known type sera. It was evident that haemagglutinins were still present in the patient's blood but, since haemolysis would continue until they were used up or the patient died from anaemia or from suppression transfusion was the rational measure in spite of the reaction *in vitro*. It was therefore decided to proceed with the transfusion and 12 ounces of blood were given very slowly with 4 ounces of 3.8 per cent sodium citrate solution and a few ounces of saline. The blood was not given much diluted owing to the obvious danger of water-logging if the plasma proteins were low which was probably the case. There was no reaction from the transfusion.

The next day 24th September his haemoglobin had risen to 45 per cent, the red cells to 2.31 million and the white cells had fallen to 11,200 per c. mm. His blood pressure was 115/75. The urine was unchanged except that there were fewer red cells. No excess of urobilin was observed and no bile pigment was present. The patient himself seemed remarkably well, indeed he had remained completely unmoved by all that had occurred, smiling happily throughout the course of his illness.

25th Sept the urine was of normal colour and contained a much smaller number of casts and no red cells. Agars tests for bile pigment and an excess

of urobilin were negative and remained so throughout. There was no clinical evidence of water retention. The haemoglobin had fallen to 42 per cent. but the proportionate drop in the red cell count was greater and the colour index was 1.1 suggesting that some haemolysis had followed transfusion, but all the laked blood had not been excreted.

29th Sept. another cross-grouping was done using a considerable excess of the patient's serum against the cells of the same donor. Very slight agglutination was seen after half an hour. The urine was now practically normal, containing only a few red cells and an occasional granular cast. There was only a trace of albumin and bile pigments remained absent. On 1st Oct. a few epithelial casts were seen for the last time and the haemoglobin was rising rapidly. Haemagglutinins could no longer be demonstrated. Ten days later the urine was clear except for a few epithelial cells and an occasional red cell while on 21st Oct. the haemoglobin was 75 per cent. It was thought that he was now well into convalescence and would make a complete recovery.

25th Oct. he was again examined in order to determine what degree of renal damage remained. He appeared well and there was no oedema. His pulse was full, however and the blood pressure had risen to 154/100. Examination of the heart showed it was enlarged, the left border being in the nipple line. Its action was forceful but there were no *bruits*. The urine contained a trace of albumin, a fair number of red cells and very occasional hyaline and granular casts were seen. Urinary dilution and concentration tests were carried out. He was unable to produce urine of a lower specific gravity than 1005 or to concentrate it to more than 1014 even after being deprived of fluids for 14 hours in tropical weather.

He received alkalis throughout and iron from the day following transfusion.

#### COMMENTARY

The case described is one in which massive haemoglobinuria followed the exhibition of quinine, atabrin and plasmoquine for sub-tertian malaria. The patient had not suffered as far as he knew from previous malarial infection neither had he an enlarged spleen and, until haemolysis occurred there was nothing unusual about his illness. He had not been taking suppressive quinine.

Since the colour index was 0.92 when a blood count was first done, it is reasonable to infer that the haemoglobin percentage was very nearly normal before the crisis occurred. So in about 36 hours the haemoglobin must have fallen by nearly 70 per cent. and most of this was rapidly excreted in the urine as there was never any clinical evidence of jaundice.

There are three points about this case which are worthy of special comment. The first is the way in which the products of haemolysis were excreted. Secondly the actual demonstration of haemagglutinins *in vitro* and lastly the nature of the damage to the kidneys.

### 1 *Disposal of the products of haemolysis*

The actual process of haemolysis took place in a very short time and probably as regards the main bulk of red cells destroyed, did not exceed 36 hours and may have been less. It is true that some haemolysis went on after this time and accounts for the small fall in the haemoglobin percentage and the greater fall in red cell count following the preliminary rise in these figures after transfusion. At first the urine was deep chocolate brown in colour but had perceptibly lightened by the 3rd day and was practically free from obvious blood pigments on the 4th. During the severe stage of the illness, the haemolysed blood was sufficient to colour the blood serum brown and it may be observed that this was brown and neither of a pink nor icteric tint. It is remarkable that no clinical jaundice was seen in spite of the vast amount of haemoglobin disposed of. The only explanations are that either the rapidity with which haemolysis occurred and the rapidity with which haemoglobin and its derivatives were excreted in the urine were so great as to preclude any great increase in the bilirubin content of the plasma or the nature of the haemoglobin derivative formed was not amenable to destruction by the reticulo-endothelial system. That there was, in fact, no excessive excretion of blood pigments through the liver is further confirmed by the observation that the urinary urobilinogen was at no time increased. It is possible that the severity of the damage to the kidneys, by reducing the threshold for haemoglobin, assisted in this speedy excretion.

### 2 *Presence of haemagglutinins in the patient's serum*

The actual presence of haemagglutinins was demonstrated *in vitro* and these persisted, in diminishing titre, for about a week after the haemolytic crisis. Auto-agglutination of the donor's corpuscles as a possible source of error was excluded and in any case the tests were carried out in warm weather.

### 3 *Renal damage*

The initial severity of the renal damage and the speed with which excretory defect supervened were marked. The urine when first examined after haemolysis—and this was probably within 24 hours of the start—did not show the presence of epithelial casts. There was a very large amount of methaemoglobin, some red cells and some renal epithelial cells. But by the next day the macroscopic picture had become that of a tubular necrosis.

From analogy with other conditions, it is unlikely that damage to the glomerular capillaries could have been in itself sufficient to cause such rapid destruction of the tubular epithelium. The absence of any great number of red cells from the urine and the absence of uraemic symptoms are sufficient to confirm this view. It follows that some toxic substance must have been present which had a direct action on the tubular epithelium. Epithelial casts

disappeared from the urine but except on one occasion, red cells were never entirely absent. When the patient was examined during apparent convalescence a month after haemolysis had taken place it was found that the urine contained a trace of albumin red cells and occasional hyaline and granular casts. This together with the observations that hypertension had set in and, most important of all, that the power of the kidneys to dilute and concentrate the urine was extremely poor show that the end result was nephrosclerosis. Presumably the amount of damage to the kidneys was so great, both as a result of direct tubular damage and possibly from glomerular destruction as well that scarring on a widespread scale followed. Renal insufficiency was the rapid outcome.

### CONCLUSIONS

The toxic effects of the drug appear to be twofold.

Haemagglutinins were produced which are not specific to the patient's corpuscles because they produced agglutination of red cells from a subject who had not received plasmoquine. The red cells of the patient were, therefore not sensitized to any product of the drug but the idiosyncrasy lies in the production of an agglutinating substance in the serum.

A toxin was produced which had a direct action on the renal tubules an action altogether separate from the process of haemolysis although possibly the substance was identical with the haemolysin.

### SUMMARY

- 1 A case is described of severe haemoglobinuria following the administration of plasmoquine to a Bantu patient suffering from sub-tertian malaria.
- 2 The presence and the subsequent disappearance of haemagglutinins was observed and is recorded.
- 3 A description is given of the severe renal damage which occurred tubular necrosis being the outstanding feature.
- 4 The significance of these observations is discussed.

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NOTE by Brigadier SIDNEY SMITH *Consultant in Tropical Medicine M.E.F.*

In his very interesting paper on Haemoglobinuria following the administration of plasmoquine Captain MANN assumes that the condition had arisen as a direct result of the toxic action of the drug. There may be more to it than that, and the possibility that this patient was suffering from classical blackwater fever plasmoquine merely acting as the trigger, must not be



lost sight of. A brief account of fourteen similar cases occurring in the Middle East during the past 18 months may be of interest —

1. Of the fourteen cases, nine occurred in Egypt, two each in Iraq and the Sudan, one in Palestine.
2. The nationalities involved were Indian, seven and one each of the following: Rhodesian (white), Greek, Polish Jew, Palestinian Jew, East African native, Basuto, Mauritan.

All the above had lived, usually for many years, in endemic foci of malaria.

It will be noted that there is not a single soldier from the British Isles in the series, although many thousands have had plasmoquine for malaria.

3. In every case they were still undergoing the plasmoquine toxicity of the standard Q.A.P. course for malaria (M.T. four B.T. two species uncertain one clinical seven).

The standard Q.A.P. course is as follows —

- (a) Quinine grains 10 t.d.s. for 3 days
  - (b) Atebrin, 1 tab (0.1 gramme) t.d.s. for 5 days
  - (c) Three days rest.
  - (d) Plasmoquine 1 tab (0.01 gramme) b.d. for 5 days.
4. 6 out of 14 died a mortality rate of 42.8 per cent.

With these cases in mind the following footnote has recently been added to our *Memorandum on the Clinical Aspects of Malaria in the Middle East*

"Several recent fatal cases of haemoglobinuria (clinically blackwater fever) have occurred in patients under treatment with plasmoquine or shortly after completion of treatment for what appeared to be benign tertian malaria.

"It is at present uncertain whether this alarming and dangerous complication is true blackwater fever occurring in cases of mixed M.T. and B.T. infection, only the latter parasite being found in the peripheral blood, or whether it is entirely due to the toxic action of plasmoquine.

"Under these circumstances it is recommended that all patients under treatment with plasmoquine receive sufficient alkali to render their urine alkaline.

"If acute haemoglobinuria then supervenes there will be less likelihood of urinary blockage due to the deposition of acid haematin in the tubules of the kidneys occurring a complication which frequently leads to oliguria or even to anuria and fatal uraemia."

This was written at a time when in the few cases then recorded only B.T. parasites had been found in the peripheral blood. Many cases of M.T. infection developing haemoglobinuria under similar circumstances have since been described, and in all probability these early cases were examples of double infection with M.T. and B.T. parasites, only the latter appearing in the peripheral blood.

## SULPHAPYRIDINE IN TYPHOID FEVER

BY

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Reports in literature on the effect of the drugs of the sulphonamide group in typhoid fever are few. LONG (1940) reported that the treatment of typhoid fever with sulphanilamide and other drugs of this group was not effective. The same statement was made by CAREY (1940). On the other hand HARRIS SWYER and THOMPSON (1939) described seven patients who were treated with sulphanilamide and were favourably influenced. Some experiments were made on mice which had been inoculated with *Bacillus typhosus*. They were treated with sulphanilamide and the results were very satisfactory (BUTTLE *et al* 1937. KOLMER and RULE, 1939).

Typhoid fever in Palestine has had for some time a relatively mild course not requiring any special therapeutic measures. During last year however it has appeared in a more severe form with a higher mortality than previously. Finding the need for more active treatment in the more severe cases we began

pyridine treatment. The duration of the disease did not seem to be shortened however in this group.

Nine other cases had no rigors, but the disease was accompanied by signs of severe toxæmia, high temperature dulling of sensorium, meteorism, etc. Two of these cases had severe diarrhoea and incontinence of urine and faeces. One of them was a young man 19 years old. He was admitted to the hospital at the beginning of the 2nd week of illness. His condition was serious. He had a diffuse roseolar eruption and severe diarrhoea. His temperature rose to 41 C. Blood culture was positive for *B. typhosus*. In spite of large doses of opium and hypertonic solution of sodium chloride intravenously as well as a continuous intravenous infusion of normal saline no improvement was obtained. On the contrary his condition was getting worse and the signs of toxæmia increased. The patient had 20 to 30 stools a day with complete incontinence. At this stage sulphapyridine was administered (This was 10 days after his admission to the hospital). He was given 5 grammes in the first 24 hours. After this his temperature dropped from 38.8° C to 35.8° C. (Chart 3.)



CHART 3.

The signs of toxæmia markedly subsided and his diarrhoea stopped completely. During the following 7 days the patient was given 3 grammes of sulphapyridine daily. His general condition improved, his fever also was kept at a lower level. Sulphapyridine was discontinued and the patient was recovering. On the 43rd day he had a relapse which lasted 18 days. In this case, as in the preceding cases it is obvious that the sulphapyridine did not shorten the period of pyrexia nor was the relapse prevented, but it had an immediate and definite effect on the toxic manifestations of the disease.

Another case to illustrate the immediate effect of sulphapyridine on the toxæmia in typhoid fever, was a boy 13 years old, who was admitted to the hospital on the 14th day of his illness. On admission the patient was highly toxic—restlessness, dulling of the sensorium, headache and nausea were the prominent features of the toxæmia. The blood culture was negative. The temperature ranged between  $38.8^{\circ}$  and  $40.4^{\circ}$  C. After 2 days of sulphapyridine treatment (the total amount given was 8.5 grammes), the temperature dropped to  $37.4^{\circ}$  C (Chart 4). Together with the drop in his temperature all the toxic

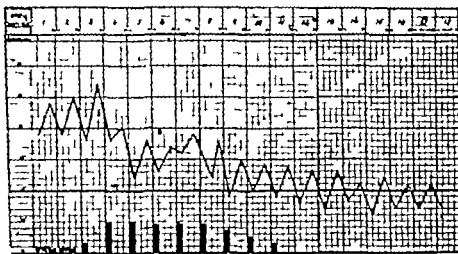


CHART 4

manifestations of the disease disappeared. The treatment was continued for 7 days more (the total amount given being 32.5 grammes). During this period the temperature gradually became normal and the patient made a speedy recovery. The impression was gained in this particular case that not only were the toxic manifestations favourably affected but also that the duration of the disease was shortened by the sulphapyridine.

The blood picture of all our patients prior to the administration of sulphapyridine showed leucopenia (4,000 to 8,000 leucocytes). Under the influence of the drug we did not see a further marked decrease in the number of leucocytes or granulocytopenia. FRIEDBERG (1941) and other authors made the same observation on patients suffering from pneumonia with leucopenia who were treated, nevertheless, successfully with sulphapyridine. It follows, therefore, that leucopenia is no contra indication to sulphapyridine therapy. The drop in leucocytes occasionally observed following its administration depends less on the original white cell count than on the individual response of the haematopoietic system to the drug.

## SUMMARY

Our observations on eighteen cases suffering from typhoid fever treated with sulphapyridine lead to the conclusion that the septic and toxic features of the disease may be favourably affected by this drug. The rigors, if present, stop and the toxic manifestations of the disease usually disappear although the duration of the disease does not seem to be shortened. Sulphapyridine may therefore be considered a valuable aid in combating certain phases in typhoid fever.

## REFERENCES.

- BUTLER, G. A. H. PARISH, H. I. McLEOD, M. & STEPHENSON DORA (1937) *Lancet* 1 681  
CAREY BENJAMIN W. (1940) *J Amer med Ass* 118 925  
FRIEDBERG C. K. (1941) *Ibid* 118 270  
HARRIS, E. H. R. SWYER, R. & THOMPSON N. (1939) *Lancet* 1 1321  
KOLLMER, I. A. & RULK, A. M. (1939) *Proc Soc exp Biol N Y* 40 615  
LONGO P. (1940) *Bull N Y Acad Med* 16

## PHENOTHIAZINE IN THE TREATMENT OF HUMAN INTESTINAL HELMINTHIC INFESTATIONS

BY

MOUNTJOY ELLIOTT M.A. M.D. M.R.C.P.I.

The pharmacology and antiparasitic action of phenothiazine (thiodiphenyl amine) in the human and veterinary fields of helminthology have been recently reviewed and summarized by DAVEY and INNES (1942). It has proved itself a powerful weapon against certain intestinal parasites of animals but as yet no careful survey as to its potentialities in the human subject has been made. Our limited observations amongst the natives of West Africa have convinced us that this drug may be as potent a destroyer of hookworms as any of the drugs at present used for this purpose. We were also impressed by its action against *Strongyloides stercoralis* parasites which up to this have been very difficult to deal with in some patients. KUITUNEN EKBAUM in Canada (1941) studied its action against threadworms and found it exercised a powerful destructive action on these worms.

### *Toxicity and Dosage*

The drug must be given in strictly controlled dosage especially to children as toxic sequelae have been reported following its use in children. Inhibition of haemopoiesis haemolysis or hepatitis were recorded (HUBBLE 1941 and HUMPHREYS 1942). I have given the drug to over seventy adult natives and have been impressed by its lack of unpleasant sequelae as compared with fifty control patients to whom santonin, oil of chenopodium or carbon tetrachloride had been given.

The American standard of dosage was put at 1.0 gramme per 10 lb of body weight. This appeared a safe adult level because I gave the phenothiazine in doses usually more than double this standard and had no cases of intolerance. Our total adult dosage varied between 20 and 30 grammes and it was spread out over a period of 4 to 5 days. Results are very poor if attempts at shock therapy are attempted by giving the total dosage in 1 day as is the custom with most other antiparasitic drugs. The reason for this has not yet been explained but there is evidence that phenothiazine acts as a tissue toxin only after it has been ingested by the parasite and not as an environmental poison. If this is the case, its action against those parasites who derive their nutrition by sucking lymph and blood from the intestinal mucosa, can only be brought about by the minute quantities of the drug absorbed into the blood stream.

*Method of Administration.*

The drug is put up in 1 gramme tablets and was given to our patients<sup>†</sup> in three equally divided daily doses after meals, *i.e.*, two tablets three times a day after meals for 4 to 5 days. It is important to give the large tablets crushed up otherwise they may be passed unchanged in the stools. The diet during the period of treatment should not be too heavy.

## ASSESSMENT OF CURE

Owing to shortage of laboratory staff we were unable to make ova or worm counts on unit bulk weight of faeces but used simple cover glass preparations instead. If two successive preparations failed to show any ova, the patient was considered cured. The first examinations were not made until at least a week had elapsed since the completion of treatment.

*Results*

On the basis of the above assessment, the following infections were considered cured by the administration of phenothiazine.

<i>Parasite.</i>	<i>Number Treated.</i>	<i>Number Cured.</i>
<i>Ancylostoma duodenale</i>	36	26
<i>Strongyloides stercoralis</i>	8	5
<i>Ascaris lumbricoides</i>	15	9
<i>Taenia saginata</i>	8	4
<i>Trichurus trichurus</i>	8	5
<i>Entamoeba histolytica</i>	9	6

## SUMMARY

Phenothiazine appears to be well tolerated by the adult native if given in accordance with the American standard of dosage. This preliminary investigation suggests that phenothiazine has an antiparasitic action against *A. duodenale* and other common intestinal parasites. A further detailed clinical investigation into its potentialities might yield much valuable information.

## REFERENCES

- DAVEY D. G. & IDOES, J. R. M. (1942). *Vet Bull* 12 (8) R. 7.  
 HUBBLE, D. (1941). *Lancet*, 2 600.  
 HUMPHREYS, D. R. (1942). *Ibid* 2 39.  
 KUTTUONG-EXAMM (1941). *Canad publ Hlth J* 22 303.

## CORRESPONDENCE

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### PARAGONIMIASIS

*To the Editor TRANSACTIONS of the Royal Society of Tropical Medicine and Hygiene*

SIR,

The case reported in a recent number of these TRANSACTIONS\* has now been re-examined, with the following result —

*Present Symptomology* —The man now states he feels very much better. The pain in the ear has almost disappeared and there is no tendency to fall over to the right side. Although he still complains of impaired hearing on the side of the cyst the attacks of cloudiness and dimness of vision have ceased. When pressure over the operation area is exerted it produces complete deafness and cloudiness of vision which clears in about 30 seconds after the pressure is discontinued.

These are his symptoms at present.

*Examination* —The right homonymous hemianopia has almost completely disappeared and the contraction of the fields of vision of the right eye has so improved that no abnormality could be found with the simple means at my disposal. Pupil reflexes and cranial nerves are normal with the exception of the 8th, while even this has improved.

I could find no hypotonia of the left arm and leg but the reflexes of the left arm were still slightly depressed. The left knee jerk could be elicited without reinforcement but was still considerably depressed.

There were no other abnormalities.

You will see, therefore that his condition has very greatly improved without any special treatment since the removal of the cyst. Can it be that we have drained an intracranial cyst which had communication to the neck? I feel this is the right diagnosis though there is insufficient evidence to make it dogmatically.

I am, etc.,

G. R. YARWOOD

Captain R.A.M.C.

\* YARWOOD, G. R. & ELAIS B. G. T. (1943) *Paragonimus* cyst in a West African native. *Trans R Soc Med Hyg* 36 347.



## DIAGNOSIS OF PERNICIOUS MALARIA.

To the Editor *TRANSACTIONS of the Royal Society of Tropical Medicine and Hygiene.*

SIR,

I have read with interest Lieut. Colonel D. KENNETH LINDSAY's letter in your last issue of the *TRANSACTIONS*\* recording some valuable guidance notes on pernicious malaria in connection with a specified community in a particularly malarious place, at a specific period.

Although not so claimed by the author these notes are valid for any place where *P. falciparum* infection is endemic since it is a well known fact that subtertian malaria is most protean in its clinical manifestations, may simulate a host of other diseases and even fool the surgeon into performing an appendicectomy for symptoms which quinine would have cured. This is corroborated by his own statement—Do not repeat my mistake of forgetting malaria and doing an unnecessary trephine.

It cannot be too strongly impressed upon newcomers into tropical medicine that subtertian malaria should always be the first condition to be excluded in all cases of collapse, cerebral irritation, coma, severe abdominal cramps, particularly gastro-intestinal symptoms (vomiting, hiccough, choleraic diarrhoea) haemorrhagic manifestations, haemoglobinuria, and indeed fever in general since a case of simple subtertian malaria is liable to develop pernicious symptoms suddenly.

While he is quite right about negative blood slides having probably sent many to the grave I must question his statement that *the microscope has little place in the diagnosis of pernicious malaria* except perhaps only in cases of black water fever in which, owing to the sudden extensive haemolysis, parasites are largely destroyed. Fortunately the diagnosis of blackwater fever hardly requires the microscope.

In all other forms of subtertian malaria, however it is agreed that pernicious symptoms are largely due to blockage of visceral capillaries by the growing trophozoites of *P. falciparum* which, from about the 8th hour after hatching and circulating tend to stick to the walls of visceral capillaries and to one another—hence their disappearance from the peripheral circulation and absence in films of the peripheral blood. But, surely there is nothing to prevent their being demonstrated by the microscope in films of visceral blood obtained by either sternal or liver puncture. This is a simple and sure method of absolute diagnosis which should be available and practised in all areas where subtertian malaria is endemic, since a diagnosis can be established within half an hour.

If parasites are absent in films of the peripheral blood and also in those of sternal marrow or blood from the liver subtertian malaria can safely be

excluded. On the other hand, owing to the fact, which Colonel LINDSAY himself points out, that *P. falciparum* is often the underlying cause of such pernicious symptoms even when some other disease co-exists films of sternal marrow will never fail to reveal its presence. Intravenous quinine will then be a logical and justified procedure. Otherwise the practice he advocates should be reserved only for occasions on which means of scientific diagnosis are not available

I am, etc.,

L. C. D. HERMITTE,  
Médecin Malarologiste Paris

Pathologist Royal Infirmary Sheffield

### "FOOD" YEAST

To the Editor TRANSACTIONS of the Royal Society of Tropical Medicine and Hygiene

SIR,

Some recent statements appearing in the Press in reference to *Torula utilis*—the new "food" yeast—give rise to some concern, with regard to its projected use as food in the tropics.

*Torula utilis* is not new though methods for improving its strain and production are new. Like any other yeast, its primary value must lie rather in the therapeutic field of medicine than in its direct use as food. Again, in spite of its apparent improved palatability, odour, appearance and miscibility this does not qualify its use as food in any real sense of the term. While it may prove of added value as a temporary expedient in time of famine or acute distress and, say as a re-enforcing agent for some natural foodstuffs it would be a serious mistake—as well as misleading—to make it a substitute or alternative to protein-bearing natural foods, as part of any long-term food policy. Some suggestions to this end, almost revolutionary in effect, have in the Press been put forward for tropical peoples, especially those of the West Indies. This is not fair to the deeper principles which are involved.

The writer who used some 10 cwt. of dried brewer's yeast in a visit to West Africa in 1937-38, and in the comparatively short period of 8 months, investigating a vitamin B deficiency state there, well remembers asking himself was he doing any real justice to nutrition by issuing such large amounts for, though effecting a temporary cure, it was not removing the cause. There is this vital difference between cure of a disease and its prevention and great care is required in treating a condition, that the cause itself is neither masked nor left in abeyance.

Again, it has to be remembered for most tropical countries, gross evidence of other deficiency diseases, such as vitamin A, scurvy, mineral deficiencies, etc., may equally co-exist. By analogy then, are these to be met with by issuing vitamin A concentrates, ascorbic acid, etc.? The

be no less a logical sequence to that already projected for *Torula utilis* and the B deficiency states.

The whole principle of applying synthetic remedies or concentrates as substitution factors for natural foods is wrong. *Torula utilis* should only be used—in its relation to food—as an extra, preferably in tropical countries, as a silent extra, without disturbing the ordinary food or habits of the people. If the West Indies are short of protein as we know they are their needs are no less pressing in development of natural protein foods, milk, meat, eggs, fish, etc. especially milk.

And in the tropics it has to be realised that even as an "extra" much of the malnutritional class will fail to benefit. For instance one suggestion which at first sight finds reasonable support and appears practical enough—that of re-enforcing wheat flour—fails to observe that one of the most pressing needs of the West Indies, particularly in the malnutrition classes, is that of wheat flour itself. Even in schools and public institutions where supervision can be controlled, and this means could be helpful great care would be required that not only was there no disturbance of customary habit by this provision as an extra only but also in propagating its use to ensure that this did not offset the proper teaching of nutrition in relation to natural foods or detract from training in production of food.

Another suggestion put forward was that this yeast could be mixed with soups. Those familiar with tropical peoples know the ordinary folk are not only extremely conservative in their methods of preparation and use of foods but generally speaking, are totally unaware of the relationship of the vitamins to food nor will they change these food habits readily to suit the instructions of laboratory findings. A good example of this has been shown in Zanzibar East Africa, in the relative refusal of the ordinary people to replace their staple coconut oil, deficient in vitamin A, with red palm oil, rich in vitamin A, even though the latter was offered free in some localities. By contrast, had ghee been offered free, it would have been accepted eagerly because here no affront was possible to their food tastes.

In short there is no short cut in the tropics, any more than anywhere else, to ensure better nutrition this can only be achieved on the same principles as evidenced for other countries.

Used in its proper perspective, and primarily of course, medicinally *Torula utilis* may have great value. Undoubtedly it will prove of great use in animal and poultry feeding. But it does not offer any form of substitute or alternative to human protein needs as food for ordinary people, nor should it delay in any way the development and production of natural foodstuffs, as is very properly if still incompletely envisaged, by the Stockdale Report for greatly increased mixed and dairy farming fish production and so forth.

I am, etc.,

D FITZGERALD MOORE.

TRANSACTIONS  
OF THE  
ROYAL SOCIETY OF TROPICAL MEDICINE  
AND HYGIENE

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VOL. XXXVII No 3 DECEMBER, 1943

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OPENING MEETING OF THE THIRTY-SEVENTH SESSION

held at  
Manson House, 26, Portland Place, London, W.,  
on  
Thursday, 21st October, 1943, at 8 p.m.

THE PRESIDENT

SIR H. HAROLD SCOTT, K.C.M.G., M.D., F.R.C.P., F.R.S.E.,  
in the Chair

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PRESIDENTIAL ADDRESS

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THE INFLUENCE OF THE SLAVE-TRADE IN THE SPREAD  
OF TROPICAL DISEASE.

BY

SIR H. HAROLD SCOTT K.C.M.G. M.D. F.R.C.P. F.R.S.E.

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Officers and Fellows of the Society—As you are all aware I have not for many years been personally engaged in tropical medical research, except historically. My predecessors were so engaged and thus were able to entertain you with detailed accounts of their personal work, new work, at all events work the results of which were new to their audience of new research into abstruse chemistry of new theories as to the causation of old diseases new forms of treatment and the like. To my great regret and, I fear your disappointment, I am not able to do this. I cannot regale you with such interesting things as one more theory on the aetiology of sprue, or the use

be no less a logical sequence to that already projected for *Torula uilis* and the B deficiency states.

The whole principle of applying synthetic remedies or concentrates as substitution factors for natural foods is wrong. *Torula uilis* should only be used—in its relation to food—as an extra, preferably in tropical countries, as a silent extra, without disturbing the ordinary food or habits of the people. If the West Indies are short of protein, as we know they are, their needs are no less pressing in development of natural protein foods, milk, meat, eggs, fish, etc. especially milk.

And in the tropics it has to be realised that even as an "extra" much of the malnutritional class will fail to benefit. For instance, one suggestion which at first sight finds reasonable support and appears practical enough—that of re-enforcing wheat flour—fails to observe that one of the most pressing needs of the West Indies, particularly in the malnutrition classes, is that of wheat flour itself. Even in schools and public institutions where supervision can be controlled, and this means could be helpful great care would be required that not only was there no disturbance of customary habit by this provision as an extra only but also in propagating its use to ensure that this did not offset the proper teaching of nutrition in relation to natural foods, or detract from training in production of food.

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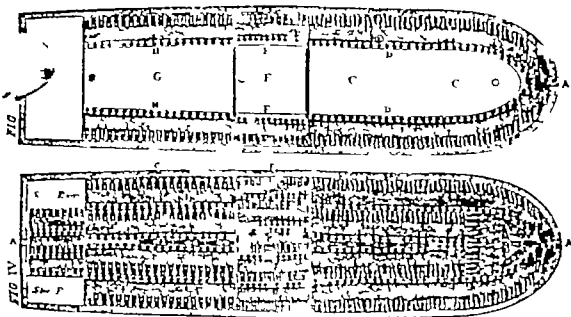
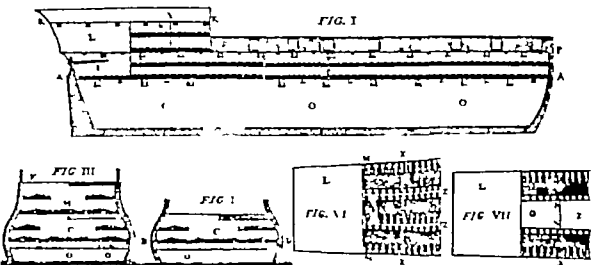
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I am, etc.,

D FITZGERALD MOORE.





Method of stowing slaves on board the ship *Brocton* Plan of Captain Perry

- |                                     |                                 |                            |
|-------------------------------------|---------------------------------|----------------------------|
| A. A. Lower Deck                    | Platforms in Boys' Room         | M. A. Half Deck            |
| B. B. Breadth of Room on Lower Deck | Women's Room                    | Platforms on Half Deck     |
| C. C. Main Room on Lower Deck       | H. H. Platforms in Women's Room | Hold                       |
| D. D. Platforms in Men's Room       | G. G. Gun Room on Lower Deck    | Upper Deck                 |
| E. E. Boys' Room                    | K. K. Quarter Deck              | X. Extra Stowage for Women |
|                                     | L. L. Cabin                     |                            |

might have to be raided to obtain the number wanted, many of the natives would die from injury starvation and disease in the jungle. Those captured would be chained to prevent their escape, with slave forks round their necks, hands fastened behind their backs and attached by a cord to the master's waist and sometimes gagged by a wooden snaffle. The heavy mortality among them on their journey to the coast was evidenced by the skeletons, slave-clogs and forks strewn along the way. Underfeeding, overworking exhaustion disease and cruelty might lose one third of the total. Much of the hardship was due to natural attempts at escape. LOVETT CAMERON observed at one time a gang of fifty-two women tied together in three lots some had children in their arms, others were far advanced in pregnancy all were laden and covered with weals, and scars—sheer wanton cruelty.

Yet a further loss, perhaps as much as another third might occur at the barracoons where the slaves were collected on the beach before transportation. Here, too the fatality would be high owing to insufficient food, overcrowding dysentery and fevers for they were kept in irons and roped in fours, legs fettered, chains round their necks. The middle passage, as the journey from Africa to the New World was called, might be fairly easy but in many cases entailed much suffering. The food was usually good and if the weather was fair they might come on deck for air and exercise, perhaps a hose bath the exercise consisting of dancing to a drum. All this was arranged not primarily for the benefit of the negro, but because sickness and mortality among them would reduce the owner's profit. On a bad ship and later when the trade was being made illegal all slave-ships were bad ships conditions must have been truly frightful. If one cargo in three got through the adventure paid so overcrowding was disregarded. In the hold were stored provisions, powder rum and so forth in the tween decks the slaves were stowed in hundreds the men forward shackled at the start of the voyage, the women and children aft, unchained. They would be thrust in till they were packed actually in contact and might stay there, if the weather was bad, for many days together. Some would die and the living and the dead would lie chained together in the dark, and hunger thirst, misery and disease in particular dysentery might, on a bad voyage, kill off 70 per cent. the average mortality on a favourable voyage was 11 to 12 per cent. Stories have been told of where the packing was so close that some would have to sit between the legs of others and the boarding above them so low—they might be in two tiers—that even sitting upright was not possible, and on arrival every conceivable distortion might be observed, as a result of the long cramped posture. If lying down each adult was allotted a space of 5 feet 6 inches long 16 inches wide and 24 occasionally 26 inches between the tiers.

Woe betide any who fell sick! According to the terms of insurance, if a death occurred on board the loss had to be borne by the owner whereas jettisoning alive came under the head of sacrifice of cargo and insurance.



was paid so those seriously ill might be thrown overboard. After the trade became illegal a slaver when chased would jettison her living cargo to delay the pursuer or cast the slaves manacled into the sea to prevent their being rescued to give evidence against their captors.

I will not harrow your feelings with more of these gruesome details. I have mentioned some so that you may understand the potentialities for transference of infection from Africa to the New World. The filth and stench of the vessels on reaching port were sometimes such that no one could be got to clean them and they had to be abandoned. Most of the slaves on arrival were very emaciated, often deformed from restricted posture, half blind from the dark and from ophthalmia and, possibly onchocerciasis and months might elapse before they were fit for sale.

I have said enough concerning the slave-trade as a trade and commercial undertaking to some a romantic story and modern minds would be inclined to regard such an appalling instance of man's inhumanity to man as mainly if not entirely romance had we not read and heard and did we not know of equally may even more, appalling systematic and sustained inhumanity in the last 4 years on the part of a nation which considered itself civilized.

Obviously the slave trade and conditions under which it flourished afforded potentialities for the spread of disease and this afternoon I would like to consider some of them.

The study is a fascinating one, for we are often too ready to assume that because a disease is, or was, common in West Africa and was recorded for the first time in the New World in the seventeenth and eighteenth centuries, therefore the latter was infected by importation from the former—a very fallacious line of argument. The problem is fascinating and, if I may be pardoned the journalistic gallicism, intriguing, and I hope the instances we take for consideration this afternoon will arouse your interest and at the same time take your minds and thoughts away for a brief period from the irksome tasks of routine practice into the realms of medical romance.

### YELLOW FEVER.

Let us start with yellow fever the place of origin of which has been the subject of much discussion, some people relying on historical records and the weighing of possibilities and probabilities, others on biological arguments.

Historically the value of the evidence of American origin must depend very largely on the meaning of terms used and the accuracy of translation of ancient records. We may dismiss, as unworthy of serious discussion, the view of AUGUSTIN that its origin was Asiatic, for he based his view on the Martinique outbreak of 1688-90 when the *Oriflamme* brought the infection, *la maladie de Siam*, or to give it its more scientific but equally misleading name, *typhus miasmatique putride jaune* on its voyage from Bangkok, disregarding the fact that the ship, blown out of its course, called at a port in Brazil where yellow

fever was raging before coming on to Martinique AUGUSTIN affirms also that Smyrna was an original focus because remittent fevers of antiquity devastated the Grecian Archipelago and the shores of Asia Minor

The chief supporters of the American origin are FINLAY (CARLOS FINLAY, not our famous G. M. FINDLAY who has done so much recently in elucidation of yellow fever problems) CAIZERGUES KERMORGANT, JORGE, and RUBERT BOYCE. HIRSCH and CHABERT I regard as neutrals. Let us take the pro-America view first. The reasons given are these —

1 After the battle of Vega Real in March, 1494 a serious outbreak of disease took place among COLUMBUS's men, with loss of one third of them.

FINLAY by a process of exclusion, maintains that this was yellow fever because other diseases with high mortality—typhus, plague, smallpox and cholera—were known to Europeans and would have been recognized by COLUMBUS

2. New colonies established by survivors of the San Domingo epidemic of 1493 (who consequently, would be, say they, immunized), namely Porto Rico and Jamaica in 1509 and Cuba in 1511, did not suffer any loss.

3 The term *xekik*, a name given to a Mexican disease in pre-Columbian days, means vomiting of blood and is translated after 1648 as black vomit, and an old Mayan manuscript, says a translation of the seventeenth century contains a medicine for *Xekik*, with black blood like an infusion of soot. *Cocolitzi* is another Mexican disease, or an alternative name for the same disease and is referred to before the coming of Europeans

4 The *coup de barre* epidemic in Guadeloupe in 1635 is regarded by FINLAY and by BÉRENGER FÉRAUD as yellow fever

5 Expeditions to tropical America often suffered a high mortality

6 Navigators make no mention of any disease like yellow fever on the West Coast of Africa prior to the discovery of America. Accounts begin to be suspicious in the middle of the sixteenth century and become more certain in the seventeenth.

7 Communication between Europe and West Africa was fairly frequent in the sixteenth and seventeenth centuries, and the disease, if it had existed in Africa, would have often been imported into Europe.

8. The slave-trade was not well established till the seventeenth century whereas, say FINLAY and BÉRENGER FÉRAUD yellow fever has been shown as existing in America ever since the fifteenth and sixteenth centuries.

Before we go more deeply into the question let us clear the ground of some of these dicta, may we call them, for they are little more? The prime difficulty

is that descriptions of disease in the early days were by laymen, the symptoms are not clearly portrayed, false causes are alleged and believed without investigation and we have, therefore, to rely largely on epidemiological factors and data—mortality climatic conditions, acclimatization, etc.

The first of these reasons, the outbreak among COLUMBUS's men after Vega Real, we have already dealt with. The second, the establishment of new colonies by survivors of the San Domingo epidemic without loss by disease, has little weight. The absence of the disease is just as likely to have been due to non-introduction of infection as to the infection being present and the people immune. Next, the terms *cocobitish* and *xelik*, especially the latter as meaning "black vomit." This name was given in 1648 to an outbreak which occurred in Mexico at the end of the fifteenth century, i.e., at least 150 years earlier. *Xelik*, it is true, means "vomiting of blood." The disease called by the translator *xelik* was known in the country certainly before the Spanish conquest, but in my belief the translator read back, as it were, his then present views into a past outbreak which the true facts hardly warranted. Records at the time of the epidemic called it *maye cimil*, and *cimil* meant not "vomiting of blood" (*xelik*), but "death from pustules," and, therefore, almost certainly smallpox and, if there was bleeding then hæmorrhagic smallpox, and the claim that it was yellow fever peters out. *Cocobitish* was a much vaguer term. It was used for smallpox in 1520 and 1538, for measles in 1531 for typhus in 1526, 1545 1463 1576 and 1595 and even for deaths from famine in 1558. To translate it therefore, as applying to yellow fever is no proof whatever that the disease was of that nature. Fourthly the *coup de barre* outbreak in Guadeloupe in 1635. That this was yellow fever has been based solely on the opinion of DU TERTRE, an historian and a Roman Catholic priest. The term means a blow with a stick, or the pain due to a cudgelling, and nobody now I believe regards it as having been yellow fever. The mortality was low. I suggest it was an outbreak of dengue. Fifthly that expeditions to tropical America often suffered a high mortality is an argument too vague to call for serious refutation from the yellow fever point of view. The cause might equally well be malaria, or typhus, or dysentery to name but a few. FINLAY's sixth reason, that navigators make no mention of any disease like yellow fever on the West Coast of Africa prior to the discovery of America and that accounts begin to be suspicious in the sixteenth and seventeenth centuries, I will speak of in a minute or two. His penultimate reason, that if yellow fever had existed in Africa in these two centuries, seeing that communication occurred between that country and Europe, why was not the disease imported into Europe is very weak, and is rather on the lines of KING CHARLES II's conundrum about the weight of a fish in and out of a bucket of water. For the answer is that history shows that it was so imported, to Gibraltar and Cadix, for example, though scarcity or absence of vectors limited its spread. Lastly that the slave trade was not well established till the seventeenth century whereas yellow fever

existed in America in that and the preceding This is an easy one to answer In the first place the slave-trade was brisk in the sixteenth century in the second the statement is a direct *petitio principii*

A word on two on his biological arguments. He avers that the mildness of the disease among negroes is not due to acquired immunization but is a racial characteristic, a degree of natural immunity This again is rather begging the question, but there seems to be some truth in it. The pure negro does seem to be less susceptible than mulattos, quadroons and octoroons, though others have observed that natives who travel to Europe, not having had the disease, are equally susceptible with the whites on returning to a yellow fever country, and negroes in non yellow fever districts are as susceptible as non immune Europeans, as shown in the Barbados and St. Kitts outbreaks of 1646 On the other hand, EYSAGUIRRE noted in the middle of last century that the Chinese settled at Lima were, like the native negroes, almost exempt from the disease

CAIZERQUES writing in 1817 bases his opinion that the disease was originally American on the statements of the Philadelphia College of Medicine as to the close relationship between yellow fever and bilious remittent fever now known to be erroneous. According to this, he affirms —

1 Yellow fever is merely the bilious remittent fever of warm countries in a severe form and arises, like it, from putrefaction.

2. Yellow fever and bilious fever are rife in the same months and subside at the same times of abundant rain and cold weather

3 They are of the same nature and differ only in degree, and one may pass into the other Yellow fever by use of purgatives,' he says " may become ordinary bilious fever and by use of unsuitable tonics ordinary bilious fever may assume all the symptoms of malignant yellow fever

4 They are equally contagious under similar atmospheric concurrences

5 Since 1793 (the date of the famous Philadelphia outbreak) the constitution of the air has imparted an inflammatory character to all the prevailing diseases

6 Yellow fever is due to local causes such as putrescence from canals, streets, etc. and to vessels loaded with vegetables in a decaying state.

7 If it be said that cases occur in persons who have not been exposed to imported contagion we can only reply that miasmatic contagion is very subtle and similar inexplicable cases occur for example, in smallpox.

CHABERT though he wrote much, contributes little, alluding to the confusion that there was between yellow fever and typhus, putrid fever continued ataxic fever intermittent and remittent bilious fever, abscess of the liver (he quotes Professor TOMMASINI in support of this) primary phlegmasia of the

stomach (in the words of Professor GIRARDIN, who held that sporadic yellow fever was essential for acclimatization) and scurvy (on the authority of Dr DALMAS). He himself makes the not very useful suggestion that yellow fever is due to "gastricity and phlogosis."

At one time, authorities on yellow fever states R. JORGE in his monograph, would call the disease American typhus, accepting the American origin as a truism, thinking they solved the problem by thus cutting the Gordian knot. Other points which JORGE adduces are that the description by LOPEZ DE COGOLLUDO of the Yucatan outbreak of 1648 is a clear-cut picture of yellow fever (but there is no mention of icterus) and that the first description by a medical man, mentioning jaundice and black vomit, is that of the Portuguese FERREIRA DA ROSA on the Pernambuco outbreak of 1685-86. JORGE affirms—but I can find no evidence to verify it—that the negro in America is almost immune, whereas in Africa he is readily attacked, and he goes on to say that

one must reject the idea that immunity among the negroes is acquired—all evidence goes to show that it is a racial gift, i.e., a natural immunity.

KIRKPATRICK states categorically, clearly taking it as established and indisputable, "the disease originated in the Gulf of Mexico, where it was known since the discovery of the New World. Next, it made its appearance in the Antilles, the eastern and western coasts of North and South America, and finally the West Coast of Africa and, at times, in Europe."

Lastly Sir RICHARD BORCE, in his three chief works—*Yellow Fever and its Prevention*, *Mosquito or Man?* and *Health Progress in the West Indies*—states, in the first, as if it were a settled fact, that yellow fever was primarily a New World disease and he repeats it in the others. Nowhere does he attempt to discuss the question. The opening words of his book on yellow fever give his view quite clearly. The fragmentary historical evidence which we possess tends to show that yellow fever existed among the native races of Central America when the Spaniards arrived. It is stated to have been known to the ancient Mexicans. It was found in Columbian times amongst the peoples inhabiting the New World. Centuries afterwards evidence points to a similar endemic foothold on the West Coast of Africa." He seems to regard it as an endemic disease in various places from the beginning. Thus, "Yellow fever was one of the established indigenous diseases when the early explorers arrived (in Central America) from Europe (page 4). "In British Honduras yellow fever was no doubt endemic in the early part of the seventeenth century at the time of its settlement in 1630 (page 6). "We can, I think, come to no other conclusion than that yellow fever was endemic in these [West Indian] islands at the time of their invasion by the Latin races in the sixteenth and seventeenth centuries," and he mentions Cuba 1620, Guadeloupe 1635, St. Kitts 1648, Barbados 1649 and so on, but, strangely enough, he says (page 15) "In the case of Barbados, the fever attacked the coloured and black population with more frequency than the white—therefore, surely a new disease, or as BORCE

puts it, 'endemic fever had long ceased to exist, without offering any evidence that it had been present there before. Again speaking of Grenada Yellow fever is said to have been introduced in 1793 from West Africa and, in consequence was called Bulam fever. It certainly could have readily been introduced but in all probability the fever was naturally endemic to this as to other islands of the group. This is mere conjecture unless some evidence is adduced in support. One last quotation from this work. On page 48 BOYCE states that whether yellow fever was first endemic in the West Indies or in Central and Southern America the conclusion is that it was endemic in both. Also yellow fever was in all probability a disease endemical to the native races of the coast [of West Africa]. BOYCE perhaps brings one point as evidence, but it is of little worth. In *Mosquito or Man?* he writes. There is every reason for supposing that yellow fever is one of the very old diseases of mankind in the New World. It is stated that it was known to the Aztecs under the name *matlazahuatl*. But, says HIRSCH who had gone into the question, there is no reason for identifying with yellow fever the Mexican pestilence under the colloquial name of *matlazahuatl* for it was prevalent almost exclusively among the natives of the country and it affected only the interior and the tableland of Mexico sparing the coast regions. It can hardly be doubted that it was typhus.

The evidence in favour of the African origin or more correctly the source whence other parts of the globe became infected has fewer supporters but, it appears to me they have the greater weight of evidence. (If I may apply a Latinism I would say that those in favour of the American origin are *multi* and their evidence *multa non multum* whereas the pro-African evidence may be spoken of as *multum* though the advocates of it are *non multi*.) This evidence may be ranged under two main heads (1) Epidemiological including historical and (2) Biological or entomological. Let us take it in that order.

It is generally acknowledged that the first intelligible account of undoubted yellow fever was that of Fray Diego LOPEZ DE COGOLLUDO describing cases in Yucatán in 1649 and the first detailed account of an epidemic in the New World that of the Fever of Olinda, a seaport of northern Brazil, in 1685-86 whereas the first to describe the disease in West Africa was SCHOTTE who in 1780 gave an account of the 1778 outbreak at St. Louis Senegal. It is not easy to say now what was the nature of the earlier epidemics in the New World for they were recorded briefly by military or other non medical men who merely noted them as interfering with their expeditions of conquest. They used vague terms such as *una peste una fiebre pestilencial el contagio la epidemia* and the like occasionally one more specific, *la modorra* meaning lethargy or stupor more likely to have been cerebral malaria or enteric fever than yellow fever.

Records of times before the Spanish Conquest in 1519 the Nahuatl records during the Conquest and for half a century after it and those of later Spanish

historians describe nothing which seems to me to resemble yellow fever and the disease mentioned by COLUMBUS as occurring in 1493 was almost certainly malaria at all events it was not yellow fever. Further the outbreaks which these records do mention are ascribed to famine and cold and occurred in the *tierra fria*, the cold country where yellow fever if introduced, would not be likely to spread. Moreover as far as can be made out the symptoms were not those of yellow fever. That of 1520 known as *taktomonatisth*, was so serious in the city of Mexico that CORTÉZ abandoned the place. The word means "having pustules," and was almost certainly smallpox, as was that of 1538. The outbreak of 1531 went by the name *asarampion* i.e., measles, also very fatal as it usually is when first introduced into a country e.g. East Africa in the 1830's, as recorded by LIVINGSTONE, and in Fiji in 1874-75 when 40 000 died of it. In 1545 1563 and 1596 very severe outbreaks occurred with high fatality but the symptoms differed much from those characteristic of yellow fever. Why they have been taken for granted as yellow fever I cannot imagine. The most striking symptoms were fever and profuse hæmorrhage from mouth, nose and anus. In Mexico alone 800,000 are said to have perished, in Tlaxala 150 000 one outbreak was prolonged during the cold season—itsself a fact militating against its being yellow fever. TORQUEMADA estimated the total deaths at 2,000 000 and he called it *tabardillo* a spotted fever of the typhus group. It was also known as *mathaltotomquis* or blue-green fever. It may have been hæmorrhagic smallpox, typhus, or louse-borne relapsing fever or all three whichever it was, the point material to my thesis is that it was not yellow fever. Moreover the Indians were the chief victims, not the Europeans, a strong point against its being yellow fever. In 1550 an outbreak known as *papera* had a high fatality. *Papera* means swelling of the neck and seems to have been some form of severe angina with adenitis, possibly diphtheria. It would appear to have been too severe for epidemic parotitis. Lastly at least the last I need mention is that of 1595 when there was a serious epidemic said to be a mingling of *papera* and *tabardillo* or as I would interpret it, anginal sore throat, perhaps diphtheria, and typhus.

Two sorts of outbreaks are described by what we may call the Conquest group of recorders, one smallpox, the other characterized by "throwing off of blood by nose and mouth," very like the fatal cases in the 1918 pandemic of influenza with complicating pneumonia. In all HERRERA's writings I can find no disease with symptoms characteristic of yellow fever.

So we come to the 1648 outbreak referred to already this was undoubtedly yellow fever the description is remarkably clear. The natives and Europeans (Spaniards) were equally attacked and the whole reads as a classical account of yellow fever among a non-immune population and there is little doubt that infection had been brought in vessels sailing between Campeche and Vera Cruz. Before the recent protection test the most trustworthy criterion of endemicity was the degree of liability of the people to contract the infection when

the virus was introduced. Judged by this standard Cuba had no yellow fever for 125 years after it was occupied then an outbreak occurred which, it is recorded, carried off a third part of the garrison and civilians, that is natives as well as Europeans.

As regards the claim that records from the New World preceded any from West Africa, this is not disputed. COGOLLUDO's account of the 1648 outbreak preceded that by SCHOTTE of the Senegal outbreak by 130 years but this has little weight as favouring priority of infection in the former because COGOLLUDO shows that the natives were as susceptible as the Europeans, and failure to describe it earlier in Africa finds a ready explanation in the paucity of Europeans and the fact that most of these were soldiers or convicts incapable of describing it. Moreover, communication between Africa and the New World was frequent in the two centuries preceding COGOLLUDO's account. Thus, in 1503 OVANDO the Governor of Hispaniola had asked that no more negroes be sent there, as they were already too numerous for good order. Again from what is known—the point has been referred to earlier—the Indians of America exhibited no immunity but contracted the infection as readily and in general had as high a fatality rate as the white men.

The history of the slave-trade itself gives no little help in solving the problem. The trade from Africa was started by the Portuguese in 1482 the slaves being obtained from the mainland. In 1482 the Bay of Arguim was their trade base. Elmina in 1482 and Angola in 1490 became centres of collection and their ultimate distribution sites were tropical America and the Spanish settlements. Between 1581 and 1640 Spain and Portugal were under one sovereign, but at first Portuguese vessels only might enter Portuguese West African ports and only Spanish vessels could trade with the Spanish ports of America. São Thiago in the Cape Verde Islands, was constituted the intermediate distributing centre, slaves from ports not under Portuguese control being taken to French, Dutch and English colonies in America. The outbreak of 1585 which proved so disastrous to DRAKE's expedition at São Thiago according to the description available, was typical yellow fever and Sir RICHARD HAWKINS writing of the Cape Verde Islands in ELIZABETH's time, notes their unhealthiness. In two times that I have been in them either cost us one half of our people with fevers and fluxes and in one of them it cost me 6 months sickness with no small hazard of life. *Aedes* might easily be imported from the Guinea Coast to São Thiago the drinking water was rain which was stored on board, and in the dwellings.

In the Gambia there have been epidemics of fever at least since the fifteenth century. We cannot say that these were or were not yellow fever but there seems to have been no change in their general character before or after the slave trade started or before or after the discovery of America. Lastly there is indirect evidence that the disease was new to the West in the fact that so often and in so many places the people had no name for it, calling it merely by the



name of the place whence they thought it had been brought, such as *maladie de Siem*, *Bulam fever*, *Oluda fever*, *Orriflamme fever* (the name of the vessel introducing infection).

Summing up the historical evidence we must, when all is considered conclude by saying that positive evidence is not sufficient for us to affirm beyond all doubt where human yellow fever originated. Owing to paucity of records, confusion of diseases, to the writers being non-medical, we really cannot say what actually were the pestilences before the arrival of Europeans. The statement that America was probably the primary site because jungle yellow fever occurs there and not in Africa is totally unwarranted.

Turning to the biological or entomological argument, A. W. SELLARDS, in STITT's great work, states "Presumably both the virus and the insect vector (*Aed. aegypti*) were brought to the New World during the days of the slave trade. [I do not like "presumably" it often presumes too much.] On entomological grounds the *aegypti* mosquito appears to be an importation into the New World since there are many species of mosquitoes more or less closely allied to *A. aegypti* in Africa, but no other member of the subgenus *Stegomyia* which is native to the Americas. JORGE goes even further and says that America had no *Stegomyia* in pre Columbian days, and that the mosquito was imported thither in ships from African ports. We may compare this with the importation of *Anopheles gambiae* in modern times. Again, in America later there was one species only *Aedes aegypti* in Africa several, and therefore, he argues, Africa is the place of origin of *Aedes*. But, and this is very important, *aegypti* is not the only *Aedes* in America, at all events now. *Aedes cinifer scapularis rubulus flavitatus terreus* and *fulvithorax* exist there some of these are infectable experimentally and *scapularis* is believed to have been the vector in the Chumash outbreak. Aside altogether from this is the fact that, fortunately the geographical distribution of yellow fever does not correspond with the distribution of its usual vector. Why has Asia remained exempt, why China? why most of the Mediterranean coast, except Leghorn? We do not know. the Athens outbreak of dengue shows the prevalence of *A. aegypti* and vessels must often have come there from Africa and America.

Whether yellow fever had its origin in West Africa or in the New World is important in so far as the incrimination of the slave-trade as introducing the disease into America is concerned, but it is immaterial as regards the wider question whether the trade was the cause of the spread of infection, for whether it was carried from Africa to America or brought back in ships returning from America to Africa, to the West Indies, to Europe, the slave-trade was the means of effecting the extension.

### LEPROSY

It is not possible to declare with certainty in what country leprosy originated, but study of available records points to its first home being Africa, the belt of

land extending across the Continent from Nigeria to Abyssinia the country where its endemicity is greatest today BRUGSCH in his *Histoire d'Egypte* mentions that it was prevalent in Egypt in the reign of HUSAPTI 2400 B.C., and we know that it has been common in Africa, Egypt and India for the past 3000 years and that it was re introduced into Egypt by negro slaves brought from the Sudan in the time of RAMESSES II 1350 B.C.

Its introduction into Europe does not concern us now, except perhaps as regards Spain and Portugal. To these it was brought first by Phoenician traders. Rome and Italy generally owe its presence primarily to Pompey's soldiers returning from the East in 62 B.C., and again nearly 2000 years later, to immigrants returning from Brazil and other parts of America. The Romans spread it to Germany at the end of the second century whence it extended to Spain in the fifth and sixth centuries and to France by invading Saracens in the eighth century. Generally speaking we may say that in Europe and the East extension has been the result of immigration to Indo-China, Siam Java, Sumatra, Borneo the Philippines and Malaya largely by the Chinese. Strictly I suppose, as Egypt was infected by slaves from the Sudan nearly 3,300 years ago this should be included in my thesis but I propose not to go outside the slave-trade between Africa and the New World. West Africa itself, it is generally believed, became infected by slaves or immigrants from the Sudan and with opening up of the interior and increase of commerce the disease spread rapidly.

America became infected from four sources Europe Asia, Africa and the West Indies. CHICO the only writer I know of who affirms that the Spaniards at the Conquest of Mexico in 1519 found cases among the natives was probably misinformed. JULIANO MOREIRA who has gone deeply into the question, has concluded that these were more likely cases of *mal del pinto*. It is now generally admitted that America was free from the disease until the Spaniards and Portuguese introduced it and when the slave trade became a thriving industry the negroes who were brought over included hundreds, perhaps thousands, of lepers, and after emancipation of the slaves indentured Indians and Chinese introduced yet more.

The story is similar in many of the Spanish colonies and settlements the slaves being not the primary but the secondary introducers and far exceeding the former. Thus, Louisiana was infected by early settlers from Spain next by slaves from Africa, later still by Acadians from Nova Scotia and imported slaves from the West Indies in the middle of the eighteenth century. HANS SLOANE reports seeing cases in Jamaica in 1687. Portuguese emigrated with their slaves from Brazil to Dutch Guiana in 1694 and within a decade other slaves were being imported from Africa to work on the plantations and within 70 years lepers had become so numerous that regulations had to be made forbidding them the streets of the towns, and in 1763 further importation of lepers was prohibited. SCHILLING, in his thesis on leprosy in 1768, noted that of

the indigenous natives only those suffered from leprosy who had had contact with negroes from Africa. French Guiana is believed to have been free from the disease until slaves from Africa brought the infection in the seventeenth century and the same applies to British Guiana. In Colombia the first recorded cases were among Spaniards from Andalusia in 1573 it was verified that Don GONZALO JIMENEZ DE QUESADA, the founder of the town of Bogotá was a leper. Later African slaves introduced more. Evidence goes to show that it was not the slave trade but the introduction of Indian and Chinese labour that was responsible for most of the leprosy in the Pacific Coast States.

Leprosy in Brazil presents a problem of no little interest. It was not known at the time of the discovery of the country in 1500 by the Portuguese Admiral CÂMARA there is no mention of it in the letters of VAS CAMINHA which give detailed accounts of the country and people. GABRIEL SOARES E SOUZA in 1587 speaks of *bombar* (yaws) but not of leprosy nor do the travellers SAINT HILAIRE, MARTIN KUPFFER, ORRIGNY HUMBOLDT mention it, nor does PISO in his medical report of 1648. How then, was it introduced, for it is prevalent enough in certain districts now? Not primarily can it be accredited to the slave trade, and even subsequently in part only. Slaves were first brought there from Africa in 1583 and in greater numbers in succeeding years, but nonetheless, leprosy if present at all, was not common, because, according to FERNANDO TERRA, these slaves had come from the interior and parts where leprosy was comparatively rare. There is little doubt that the early introduction was mostly by the Portuguese themselves from Europe and, to a less degree, by the Dutch, French and Spaniards. As early as 1419 leprosy was common among the Portuguese in Madeira and the Conquistadores were the first to introduce the infection. Not only in Madeira but in Portugal itself leprosy was known to be very prevalent at the time as for the French contribution, marines coming to Brazil between 1555 and 1700 were recruited chiefly from Normandy, Pas-de-Calais, and Brittany and the disease was rife in Normandy in fact, French sailors from Normandy brought leprosy to Canada. Slave importation, however greatly added to the number of lepers. By 1630 less than half a century after the trade had included Brazil, practically one fourth of the population (14 000 out of 57 000) were slaves from Africa. The ports of entry Rio de Janeiro, Bahia and Recife, showed the highest prevalence, so much so that by 1637 an appeal for control of lepers was put forward in Rio de Janeiro. By 1710 half Rio's population of 60 000 were slaves, and by 1851 of the population of the Province, a little over half a million nearly 300 000 were slaves.

In the case of the West Indies the story is very similar to that of South America—primary introduction by Europeans, Spaniards and Portuguese, when the islands were colonized and traffic arose between the islands and the mainland. The actual introduction is supposed to have taken place from Martinique or Cuba about 1776. Later of course, much wider extension was brought about by the slaves imported directly from Africa.

## YAWS.

It was the widely if not generally held opinion at the beginning of the nineteenth century that yaws originated in West Africa and that the slave-trade was the means of importing the disease into other places where it is now endemic. Even at the end of the last century J S WALLBRIDGE and C W DANIELS in their consideration of NICHOLL'S report on yaws in the West Indies, state categorically "The disease as far as the West Indies are concerned, is of African origin," but DANIELS goes on to say that the West Indian yaws is identical with the *coko* of Fiji and he saw many cases of both. Deeper investigation throws much doubt upon this in fact from all the evidence I have been able to obtain, it would appear that when tropical medical history began with framboesia, yaws existed in many regions of the world as far apart as the east is from the west. OVIEDO Y VALDÉZ (1478-1557) in his *Historia general y natural de las Indias* records meeting it in Hispaniola. PISO in 1648 notes it in Brazil, under the name *bubas*. LABAT in the seventeenth century speaks of it in the West Indies, and BONTIUS (1592-1631) in the East Indies at the beginning of the same century. The essential difficulty in coming to a definite decision arises in the fact that nearly all the references to it are in the writings of the late eighteenth or early nineteenth centuries, by which time negro importation had been going on for 250 years or more. But the fact of its prevailing in the East—the Moluccas, Java, Sumatra, Celebes, Fiji and Samoa—multitudes strongly against the view of West African origin. OVIEDO'S account, moreover, refers to Hispaniola at the time of its first colonization by the Spaniards prior to any negro importation and SIGAUD writing on the diseases of Brazil, speaks of a manuscript in the Royal Library at Rio de Janeiro and dated 1587 which treats of yaws in that country.

The fact—it appears to be factual—that the disease was present in the West before Columbian days concerns, of course, the question of its primary introduction only. There can be no doubt that importation of infected slaves would contribute much towards spreading the disease for it is known that epidemics of it occurred on slave ships. During slavery days fresh cases were being constantly imported and they became so numerous that they were segregated in yaws houses in many West Indian islands. (There was some confusion at times between yaws and leprosy and the same houses were used for both.) After emancipation these houses were abandoned the inmates scattered and became foci for other cases all over the country. We may sum up by saying that yaws was probably autochthonous in Hispaniola, Brazil, Fiji, Samoa and West Africa, and imported into the West Indies by slaves.

## TRYPANOSOMIASIS

African trypanosomiasis, negro lethargy was certainly carried to the West Indies by slaves but the fact was noticed that the creoles were never attacked,

only the negroes, and of these only such as had themselves been brought over as slaves, that is, others born in the islands, even if their parents were victims, were not attacked, though the disease might not show itself until the subjects had been in the islands for a considerable time. The natives themselves in Africa were aware of the significance of the enlarged glands in the neck—known later as Winterbottom's sign—for the Mandingoes in the Gambia used to cut the neck stones of the boys to prevent the occurrence of sleeping-sickness later in life. Whether the operation was effectually preventive I do not know but I imagine not.

Several writers have recorded cases in the West Indies and South America. MOREAU DE JOUKNÉ in 1808 saw them among slaves in the Antilles, as did DANGAIX in 1861. NICHOLAS in 1863 saw five cases among 1,200 negroes in 9 months and he thinks that one in every 100 deaths among negroes on the voyage from the Congo to the West Indies was due to negro lethargy. GAIGNÉRON and GRIFFON DU BELLAY recorded others 2 years later and GUÉRIN of Martinique, in his Paris thesis, 1869 noted 148 cases among slaves imported from the Congo in the course of 12 years. GORE had seen cases among negro soldiers in the Bahamas, and RIBEIRO among negro labourers in Brazil. These were all cases which had escaped recognition in the early stages, for the traders knew the symptoms and the high mortality among those affected and refused to buy negroes with swollen neck-glands. The slave-trade therefore, was responsible for transporting cases, but not for spreading the infection in the West because, fortunately there were no suitable vectors, no *Glossina*, in the New World.

I do not know whether reduced bugs exist in West Africa—entomologists will be able to tell us—if they do not this fact may analogously explain why Chagas's disease, as we now call it, American trypanosomiasis, was not brought from South America to Africa, bearing in mind, of course, that until Sierra Leone was founded as a slave settlement and Liberia established for repatriated slaves in 1820 the traffic in slaves was a one way traffic only.

### LEISHMANIASIS

As I have said above, we must guard against the inference that because a morbid condition, or a causative organism, is found in Africa and in the New World the latter became infected by importation from the former. A good example is cutaneous leishmaniasis. It is present as *boston d'Orient* in the East, in Asia Minor along the Mediterranean littoral, in Southern Russia, India, China (Hunan), in Africa, Tunisia, Egypt, the Sudan, the French Congo, Nigeria and the West Coast down to Angola. In the New World it occurs in Brazil, Peru, Guiana, Paraguay, Bolivia, São Paulo, the Argentine and Mexico. That it can be transported is proved by J. N. WRIGHT's case—he saw in Boston a child who had come over from Armenia and was thought

to have contracted the infection there. Though the dates of all these recordings in the New World are of the present century the condition must be of old standing in South America, for ancient Inca pottery depicts figures with the facial mutilations of *espundia*.

*Mal del pinto* has a fairly wide distribution in the New World—Mexico, Colombia, Venezuela, Ecuador, Chile, Peru, Guatemala, Brazil, Cuba—and some have thought that, as a spirochaetal disease, it might be grouped with yaws, prevalent among slaves brought to America. There seems to be little to support this, for we never hear of a case in the negroes of Africa. It may well be that the slave-trade did assist in its spread by transporting from one part of the New World to another slaves who had already acquired the disease, from Cuba to Brazil for example, but this is pure hypothesis.

### DENGUE.

As regards dengue there must be more than a little doubt. We are usually given to understand that the earliest account of the disease is that by GABERTI of the outbreak in Cairo in 1779 but I for one do not feel convinced that this was dengue. He calls it *mal de genoux*, but mentions neither secondary fever nor rash. Though these may not always be present, it is unlikely that they would be absent from all or even the majority of cases in one outbreak. RUSH of Philadelphia, was the first to describe it clearly under the name break-bone fever in 1780. From the early years of the nineteenth century outbreaks were reported from many tropical and subtropical regions—India, Spain, Tripoli, North and South America, the West Indies. I have only one suggestion in support of the possible transference of the disease by a slave-ship and this is the Guadeloupe outbreak in 1635, which, if it was dengue antedated GABERTI and RUSH by nearly a century and a half. I refer to what was called *coup de barre*, which some authorities, as I have already mentioned, have regarded, and do still regard, as yellow fever in my opinion on very inadequate grounds. The disease was characterized by violent headache, throbbing vessels, difficulty in breathing, pain in the limbs and a feeling of general bruising as after a cudgelling—hence the name. The mortality was low itself contra indicating yellow fever. Another argument sometimes adduced is that it was not a new disease even then for the natives had a name for it, *repoulicadatina*. This, too, means a blow with a stick and is just as likely to be a Carib adaptation of the French term as *coup de barre* the French equivalent of the Carib word.

### SMALLPOX

Mention may be made in passing—I am not going to discuss it—that according to CHISHOLM smallpox, whether mild or confluent and malignant, has 'in every instance been introduced [into the West Indies] from the coast of Africa by slave ships.

## HELMINTHIC INFESTATIONS

Lastly there are certain helminthic infestations which owe their spread to the slave-trade, forms of filariasis and rectal schistosomiasis. One or two of these may be considered briefly—time limits my going into the subject in detail.

*Wuchereria bancrofti* is very widespread. RHAZES and AVICENNA, Arabian physicians, wrote of it in the ninth and tenth centuries, and it is said to have been known to Hindu writers 1,500 to 1,600 years earlier. It is found in North and South America, in Australia, India, South China, Japan, the Dutch East Indies, Samoa, and in West and Central Africa. We cannot even conjecture the original home of this worm. DEMARQUAT in Paris, was the first to demonstrate the embryo in the hydrocele fluid of a patient from Havana in 1863. WUCHERER three years later found it in the chylous urine of a man from Brazil. LEWIS in 1872, in the blood of a Hindu in India. the adult worm was seen by BANCROFT in Australia in 1876-77 and MANSON in Amoy worked out its life history so the chain of discovery may be said to be cosmopolitan.

DANIELS discovered the adult of another filaria, *Acanthocheilonema perstans* in British Guiana, and MANSON the embryo in the blood of Congo natives in 1891. (For a time he was inclined to regard it as the cause of negro lethargy.) It is very common in the Congo, Nigeria, Sierra Leone, the Gold Coast, the Ivory Coast and the Cameroons also in Rhodesia and Uganda, but these do not concern us at present. It has been reported in South America, Venezuela and Trinidad, in the Amazon Valley and northern Argentina. Considering how prevalent it is, and was, in the slave regions of Africa there is a high degree of probability that the trade initiated, it certainly fostered, the spread of infection.

*Loa loa* we may certainly regard as slave-imported. *Loa loa* the eye worm of Africa, was known to PIGAFETTA in the Congo at the end of the sixteenth century and MONGIN in 1770 removed one from the eye of a negress in Haiti. Other cases all in imported African slaves, were seen in Brazil, French Guiana and Haiti. The infestation was, clearly imported but whether it spread after importation is less certain because all cases reported in the New World are thought to have contracted the infection in the endemic areas of Africa.

*Dracunculus* has been known for a long time. It is believed that the "fiery serpents" which attacked the Israelites when Moses took them from slavery in Egypt were *Dracunculus medineus* and, according to STIRT it was suggested that Moses taught the sufferers how to extract them by winding round a piece of stick. His pupils, if so, do not seem to have been very apt because the fiery part comes when the worm is broken by over zealous or unskilful attempts at extraction. PAULES of Aegina mentions it, but does not think it is a worm at all, but a nervous concretion resembling a worm and only appearing to move. PIGAFETTA, ever a keen observer (his seeing *Loa loa* has already been mentioned), saw it in the Congo and illustrates it in the account of his travels.

The endemic foci of *Dracunculus* are widespread the Nile Valley, Uganda, Equatorial Central Africa, West Africa, Persia, India. After it had been introduced into the New World cases began to be reported in the Guianas, the Caribbean West Indian Islands San Domingo (by PERÉ and POUPPÉ-DESPORTES), Jamaica (by SLOANE), Barbados (by HILLARY) and Martinique (by SARAVÉSY) and in Southern Brazil. These records all come from the time when negroes were being imported from West Africa. Since the importation ceased there have been practically no more reported cases, except from a very few centres of which Curaçao appears to be one and Feira da Santa Anna in the Province of Bahia another. This last is particularly interesting because in 1849 two caravans encamped by a stream there and, though warned against it by the natives, the travellers used the water for drinking (the record specially mentions that nobody bathed in it) a few months later all the party fell ill except a negro who had refrained from drinking the water.

All writers on this infestation in Brazil, Guiana, the West and East Indies and Egypt agree that dracontiasis was unknown there before negro importation and after that time most of the cases recorded are in Africans. When the trade ceased and with it intercourse between Africa and the New World cases became fewer and from many of its former haunts none was reported. Infestation of Bombay is attributed to imported negro troops similarly Madras in 1834 but these have no connection with the slave-trade and nothing further will be said about them now.

*Schistosomiasis*.—For a time after BILHARZ's discovery of *Schistosoma haematobium* in 1851 the lateral spined ova were thought to be due to accidental distortion of the terminal spined when passing through the tissues. Then, in 1903 MANSON thought it must belong to a distinct species when he found these eggs in the faeces of a patient from the West Indies who had never suffered from haematuria. To trace the intermediate steps is not germane to my subject, suffice it to say that the distinction was eventually proved in 1916-18 by the experimental work and researches of Prof R. T. LEIPER, showing that the intermediary snail of the lateral spined variety was a *Planorbis* a different genus from that of the terminal-spined, the *Bulinus* and that the two species of schistosomes differed morphologically.

*Schistosoma mansoni*, it is generally agreed was originally a West African species occurring in Senegal, French Guinea to Lake Chad, also in Liberia and Sierra Leone the Belgian Congo Tanganyika and parts of East Africa. Slaves brought from Africa have introduced it into Brazil, Venezuela, Dutch Guiana, St. Kitts and other West Indian islands—St. Lucia, Nevis, Montserrat, Antigua, Guadeloupe and Martinique. In some of these the infection rate is high. Incidentally we may note that in St. Kitts the infestation is far from uncommon in *Cercopithecus sabaeus* the so-called green monkey itself an importation from its home in West Africa.



## HELMINTHIC INFESTATIONS.

Lastly there are certain helminthic infestations which owe their spread to the slave trade, forms of filariasis and rectal schistosomiasis. One or two of these may be considered briefly—time limits my going into the subject in detail.

*Wuchereria bancrofti* is very widespread. RHAZES and AVICENNA, Arabian physicians, wrote of it in the ninth and tenth centuries, and it is said to have been known to Hindu writers 1,500 to 1,600 years earlier. It is found in North and South America, in Australia, India, South China, Japan, the Dutch East Indies, Samoa, and in West and Central Africa. We cannot even conjecture the original home of this worm. DEMARQUAY in Paris was the first to demonstrate the embryo in the hydrocele fluid of a patient from Havana in 1863. WUCHERER three years later found it in the chylous urine of a man from Brazil. LEVITZ, in 1872, in the blood of a Hindu in India. the adult worm was seen by BANCROFT in Australia in 1876-77 and MANSON in Amoy worked out its life history so the chain of discovery may be said to be cosmopolitan.

DANIELS discovered the adult of another filaria, *Acanthocheilium perstans* in British Guiana, and MANSON the embryo in the blood of Congo natives in 1891. (For a time he was inclined to regard it as the cause of negro lethargy.) It is very common in the Congo, Nigeria, Sierra Leone, the Gold Coast, the Ivory Coast and the Cameroons also in Rhodesia and Uganda, but these do not concern us at present. It has been reported in South America, Venezuela and Trinidad, in the Amazon Valley and northern Argentina. Considering how prevalent it is, and was, in the slave regions of Africa there is a high degree of probability that the trade instigated, it certainly fostered, the spread of infection.

*Loa loa* we may certainly regard as slave imported. *Loa loa*, the eye worm of Africa, was known to PIGAFETTA in the Congo at the end of the sixteenth century and MOYGIN in 1770 removed one from the eye of a negress in Haiti. Other cases, all in imported African slaves, were seen in Brazil, French Guiana and Haiti. The infestation was, clearly imported but whether it spread after importation is less certain because all cases reported in the New World are thought to have contracted the infection in the endemic areas of Africa.

*Dracontossis* has been known for a long time. It is believed that the "fiery serpents" which attacked the Israelites when Moses took them from slavery in Egypt were *Draconcus medius* and, according to STITT it was suggested that Moses taught the sufferers how to extract them by winding round a piece of stick. His pupils, if so do not seem to have been very apt because the fiery part comes when the worm is broken by over zealous or unskillful attempts at extraction. PAULUS of Aegina mentions it, but does not think it is a worm at all, but a nervous concretion resembling a worm and only appearing to move. PIGAFETTA, ever a keen observer (his seeing *Loa loa* has already been mentioned) saw it in the Congo and illustrates it in the account of his travels.

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But I must not weary you. There is always a fear that when one is in a position to talk without likelihood of interruption to a kindly audience one may abuse the privilege. Besides the conditions I have mentioned there are others, such as ackee poisoning due to ingestion of a fruit native to West Africa, brought thence to Jamaica in a slave-ship in 1778—evidence in favour of the African origin of alastrim and amoebic dysentery would provoke interesting discussion, but my time is up and I end by expressing to you my gratitude for your indulgence towards my desultory remarks and my hopes that this attempt to take your thoughts for a short period from busy practice by delving into the past has been both a relaxation and an interest.

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Col S P JAMES proposed a Vote of Thanks to the PRESIDENT for his most interesting Address. This was seconded by Prof P A. BUXTON and carried unanimously

## COMMUNICATIONS

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### JAUNDICE OF OBSCURE ORIGIN IN EL OBEID KORDOFAN PROVINCE SUDAN\*

BY

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AND

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*Sudan Medical Service*

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Jaundice is a common clinical condition in the Sudan, and many cases are treated in the hospitals during the course of the year. Among these cases there is always a large group for which no definite cause can be discovered, and which are usually labelled "catarrhal jaundice." Epidemics have been recorded by WHITEHEAD and CROUCH (1926), KIRK (1938) and others, and the senior writer has observed outbreaks in Juba, Malakal, and the Blue Nile province. Some years ago one of us observed a small outbreak which was associated with yellow fever immunization (cf FINDLAY and MACCALLUM 1938). In the course of yellow fever investigations in the Sudan during the last 8 years we have several times been led into confusion by cases of obscure jaundice in which the clinical features often resembled yellow fever but in which all investigations failed to give any clue to the aetiology other than showing that yellow fever and various other well known causes of jaundice could be excluded.

The present communication is an account of forty-six such cases which were seen in El Obeid hospital from November 1940 to July 1941. Added interest attaches to the present paper because the epidemic of yellow fever described by KIRK (1941) and another of relapsing fever (cf FINDLAY, KIRK and LEWIS 1941) were raging in the Nuba Mountains district of the same province during the early part of the period in which the cases here recorded

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## TERRAIN AND POPULATION.

were seen. It may be added that this is not the first occasion on which obscure jaundice has been observed in El Obeid. In October 1933 within a few weeks of arrival in the Sudan, one of us was posted to El Obeid and observed there a series of similar cases, with at least four deaths.

El Obeid is the capital of Kordofan Province, and is situated approximately 200 miles south of Khartoum and 200 miles west of the White Nile in the midst of rolling sand-dune country.

The climate is excessively dry for at least 6 months of the year and during three of these—April to June—dust storms are common. There is a short rainy season of about 2½ months from July to mid-October and the average annual rainfall over the past 15 years has been 14 inches. During the rainy season the countryside is clothed in vegetation and large areas are intensively cultivated, the main crops being millet and sesame. With the advent of the dry season the country dries up rapidly becoming a dusty thirsty land, thinly covered with thorn scrub and with groups of acacia and similar trees, and of baobabs.

The population of El Obeid town is estimated at 38,000 some 26 000 are derived from the local Arab tribes, the majority of the remainder being a shifting population of westerners deriving from French Equatorial Africa and the West Coast. Most of these people start out from their homes on the pilgrimage to Mecca. Some settle and work for a few years in El Obeid and other towns before resuming their journey others settle permanently. The hospital in El Obeid serves also a wide surrounding area with scattered villages. The people of the town itself get their living from the various trades and industries in the town, while those outside are mainly agricultural.

The standard of living is, in the main, very low. The body louse and the bed bug are such common inmates of every household as to be unnoticed by many of the inhabitants. Sandflies are common during the months February to June. Flies are a perpetual menace throughout the area, particularly in the town itself. The dysenteries both amoebic and bacillary are common. Epidemics of pneumonia and influenza occur with great regularity. There are occasional outbreaks of relapsing fever and cerebrospinal meningitis. Malaria is endemic, but is only common towards the end of the rainy season. Anopheline and culicine mosquitoes are frequent only during the rains, and are at no time a serious problem. *Aedes aegypti* is controlled in the town by frequent house-to-house inspections, and the aedes index is constantly less than 1 per cent. In the villages around there is less rigid control, but fairly frequent inspections are made. The northern boundary of the area in which yellow fever is endemic lies some way to the south of El Obeid (cf. FINDLAY *et al.* 1941). The Nuba Mountains area, in which occurred the epidemic of June, 1940 to January 1941 lies to the south and east of the town.

## INCIDENCE.

The forty six cases of jaundice here described fell into two distinct clinical groups, showing differences in symptomatology which are described below

The monthly incidence and mortality in each group is shown in Table I. Little inference can be drawn from this seasonal distribution as owing to the authors enforced absence from El Obeid the observations could not be continued over a whole year. A number of cases occurred in October, 1940 and

TABLE I  
INCIDENCE AND MORTALITY IN FORTY SIX CASES OF JAUNDICE.

	Nov	Dec.	Jan.	Feb.	Mar	Apr	May	June	July	Total.
Group I										
Cases	6	—	1	—	—	1	4	1	5	18
Deaths	—	—	1	—	—	1	1	—	1	4
Group II										
Cases	1	—	—	—	—	—	9	2	9	23
Deaths	1	—	—	—	—	—	1	—	—	2

a few in December but as these did not come under our personal observation they could not be included. The gap in February and March is a real one as no cases of jaundice came to the hospital during these months. It is probable therefore, that the maximum incidence was from mid-April to early December and only a few cases occurred during the cool dry season.

There was a large preponderance of male patients in the series but no significance is attached to this. The age incidence is shown in Table II.

TABLE II  
AGE INCIDENCE IN FORTY-SIX CASES OF JAUNDICE

Age.	Group I	Group II
0-10	2	—
11-20	2	3
21-30	9	9
31-40	6	13
41-50	1	3

Only on two occasions could any connection be traced between cases. One was in Cases 20 and 22, quoted below and it is doubtful if there was any direct connection. In the other a man who was a constant visitor to the sick

room of one of the cases himself went down with the disease after only a few days. Because of the short interval—4 days—between the onsets in these two cases it is thought that a common origin is more likely than direct transmission from one to the other.

It may be mentioned that approximately 2 months after leaving the area one of us was admitted to hospital suffering from a severe attack of catarrhal jaundice. He had not, to his knowledge, been in contact with other cases during the intervening 2 months.

## CLINICAL FEATURES AND COURSE OF THE DISEASE

### GROUP I

Eighteen of the cases, with four deaths, fell into this group giving a mortality of 22 per cent.

The symptom complex was very similar to that described by KIRK (1941) in the yellow fever epidemic, so much so that the six cases which occurred in November just after the epidemic in the Nuba Mountains was finally proved to be yellow fever were considered also to be possible cases of this condition. Later this was disproved, but at the time it had an important bearing on the control measures which were being instituted.

The cases in this group were characterized by pyrexia, headache, restlessness, transient albuminuria, and the small pointed tongue, clean at the edges, which KIRK found to be such a constant sign in cases of yellow fever. Injection of the conjunctivae was noticed in some cases. Jaundice developed from the 4th to the 6th day of the disease, cleared fairly quickly in the milder cases, but deepened rapidly in the more severe and fatal cases.

Black vomit occurred in one fatal case, and blood stained vomit in another. In no other cases was there any vomiting, and the cases in this group were remarkable for the absence of abdominal symptoms. The stools showed little variation in colour from the normal.

In only three of the cases was there any enlargement of the liver, and in only one was the spleen palpable.

All types of cases were seen, from the comparatively mild to the severe and rapidly fatal. The following are brief notes on the four fatal cases, and on two non-fatal ones which were typical of the group.

#### CASE 8—Female aged 35

The history was taken from a male relative. There had been slight fever, headache, restlessness and sore eyes for 4 days. On the 5th day the fever became more pronounced, yellowness of the conjunctivae was noticed, and she started vomiting: there had been no vomiting before this. She rapidly became worse, and was brought to hospital in a comatose condition. On admission she was deeply jaundiced and comatose and black vomit was dribbling from her mouth. Temperature was 104.6° F. She died the following day without regaining consciousness.

A specimen of liver tissue obtained from this patient by vicerotomy after death showed a complete and extensive hepatic necrosis. The normal structure was disorganized,





FIG. 1

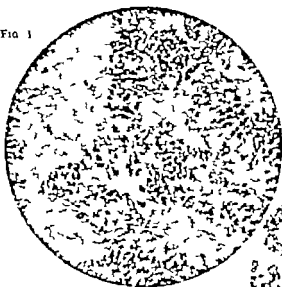


FIG. 3



FIG. 2

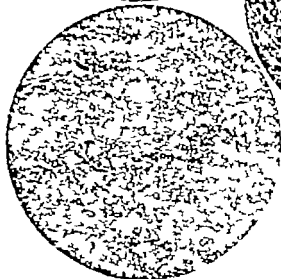


FIG. 1—Liver of Case 16 showing a well marked central necrosis.  $\times 60$  approx.

FIG. 2—Liver of Case 22 showing complete disorganization of the liver structure, with diffuse cellular infiltration.  $\times 80$  approx.

FIG. 3—Liver of Case 33 showing diffuse fibrosis, cellular infiltration, and groups of regenerating liver cells many of which show vacuolation.  $\times 80$  approx.

with almost total disappearance of the parenchyma only isolated liver cells and a few small groups remaining. Some of these remaining liver cells were small and appeared to be atrophic others were swollen and vacuolated staining irregularly and showing various degrees of nuclear and cytoplasmic degeneration. Many of them had a foam like appearance (fat globules). Occasional multinucleated cells were seen but they also were vacuolated and no mitotic figures were evident. Throughout the section generally the polygonal cells were represented by shapeless masses of debris and faintly staining pinkish globules. Typical eosinophilic degeneration and councilman bodies were not evident. The bile ducts had suffered less than the polygonal cells, but they showed no evidences of proliferation. Kupffer cells containing small granules of black pigment and larger amounts of golden brown pigment were prominent in all parts of the tissue. There was also a very definite cellular infiltration principally mononuclear most marked in the periportal regions (that is in the vicinity of the surviving bile-ducts) but also extending diffusely among the necrotic remains of the liver cells throughout the whole section. Fibrosis was not marked, nor was bile stasis and haemorrhages were absent.

#### CASE 16—Female aged 32

Headache, sore eyes and restlessness for 4 days. Fever and jaundice noticed on the 5th day. On admission to hospital on the 6th day the temperature was 102.2 F. There was deep jaundice and the patient was drowsy. She complained of intense headache. Neither spleen nor liver was palpable, and the patient did not complain of any abdominal symptoms nor could any sign of abdominal tenderness be elicited. The patient became comatose and on the 8th day just before death there was some bloodstained vomiting.

Paraffin sections of a liver specimen obtained after death by viscerotomy revealed a well marked central necrosis. Some of the central necrosed areas were intensely haemorrhagic, containing also mononuclear and Kupffer cells with ingested pigment. In others haemorrhagic change was not marked. The remaining liver cells showed a certain amount of vacuolation and diffuse fatty change but not more so than is often found postmortem in livers which are passed as normal in the Sudan, where autolytic changes may occur rapidly. The structures in the portal tracts were substantially normal except for a minor degree of round celled infiltration concentrated in places into minute foci. This had the appearance of being of some duration. It was associated with a mild degree of fibrosis and was possibly unconnected with the necrotic lesions.

#### CASE 22.—Male aged 22

Only a very scrappy history could be obtained. The patient was a soldier in the French colonial troops who had been in El Obeid for a fortnight, and was said to have been ill with fever, headache and jaundice for 3 days when he was admitted to hospital. On admission he was comatose and deeply jaundiced and he died within 24 hours of admission.

A specimen of liver was obtained after death by viscerotomy. Paraffin sections showed a complete and extensive hepatic necrosis with disorganization of lobular structure. Bile stasis and haemorrhagic changes were absent. The general picture was similar to that in Case 8 except that pigmented Kupffer cells were less evident although inflammatory changes were more prominent. Infiltration with lymphocytes and other mononuclear cells was more generally distributed, and more intense and there was quite a well marked (probably pre-existing) deposition of fibrous tissue in the portal tracts. There was no evidence of regeneration of polygonal cells. The bile-duct epithelium appeared prominent, but this was probably due to the absence of the normal pictorial background rather than to proliferation.

#### CASE 33—Male aged 25

Malariae headache and pains in the back for 3 days. On the 4th day the patient became worse, and jaundice developed. On admission to hospital on this day temperature was 101.8° F and jaundice was marked. There were no abdominal symptoms and neither

the liver nor the spleen was palpable. Patient was restless and complained of headache. The urine contained some albumin. The patient rapidly became worse, the temperature mounted, the jaundice deepened and coma supervened. He died on the 6th day of the illness.

Paraffin sections of a liver specimen obtained after death by viscerotomy showed the features of a subacute necrosis.

The parenchyma cells were distributed in scattered groups separated by young connective tissue with numerous inflammatory cells. The lobular structure could be clearly recognized in some places. Where this was so, marked increase in the periportal connective tissue was evident, and the central vein was separated from the parenchyma cells by an ill-defined zone of loose connective tissue. In other places the groups of hepatic cells were arranged haphazardly or in irregular trabecular pattern, and surrounded by connective tissue of varying density in which were abundant clusters of lymphocytes. The parenchyma cells were of middle size or small, closely packed together and with prominent nuclei. In some places their appearance was intermediate between that of bile duct epithelium and liver parenchyma. These features are perhaps to be interpreted as signs of regeneration, although many of the cells showed vacuolation. There was no evidence of regeneration occurring from the interlobular bile ducts, which appeared normal. Particles of imbedded bile in the cells and in the intercellular canaliculi were evident. Haemorrhages were absent, and very little debris or necrotic material was to be seen.

#### CASE 20—Another French soldier. Male, aged 28

This case occurred a week before Case 22, and although they were in the same company they were not living in the same tent. Again it was impossible to obtain a detailed history. He had had fever and headache for 3 days, and was brought to hospital on the 4th, a jaundice had developed. On admission, the temperature was 101° F. and the pulse was 86 per minute. The conjunctivae were yellow. There were no abdominal symptoms, and the liver and spleen were palpable. The stools were normal in colour and consistency. The urine contained a trace of albumin on this day and the next. His tongue was small and pointed, highly furred in the centre and clean at the edges.

His temperature fell by 1/2° on the 5th, and was normal by the 7th day. The jaundice deepened slightly for 2 days and then began to clear until on the 16th day no discoloration of the conjunctivae was noticeable.

#### CASE 35—Male, aged 33

Fever and headache for 3 days. Jaundice developed on the 4th day. There was only slight pyrexia, and the temperature was normal by the 6th day. The jaundice was never severe and the conjunctivae were clear by the 10th day. There were no abdominal symptoms, and the stools were normal in appearance. There was a trace of albumin in the urine on the 4th and 5th days. The tongue presented the same appearance as in Case 20.

### GROUP II

The remaining twenty-eight cases, with two deaths, fell into this group giving a mortality of 7 per cent.

The symptom complex was characterized by lack of fever by enlargement of the liver abdominal discomfort or pain, sometimes of a colicky nature and light, or even clay-coloured, stools. In only two cases was any albuminuria found, and one of these was found to be infected with *Bilharzia haematobium*. The tongue was large and flabby and thickly coated, in very sharp contrast to the cases in Group I.

Pyrexia was noted only in five cases, and two of these were fatal. Vomiting occurred in five cases including one of the fatal ones. Nausea was present in a number of others, while twenty four of the cases complained of abdominal pain. In nineteen cases the liver was found to be enlarged and four of these complained of tenderness on palpation. In twelve the spleen was palpable.

There follow notes on four cases two of which were fatal.

#### CASE 7—Male aged 28.

Malaise abdominal pain and constipation for 4 days. Jaundice was noticed on the 5th day and the patient came to hospital. On admission the temperature was 99.6° F and it never rose above 100. There was a marked degree of jaundice. The patient complained of vague bodily pains but there was no complaint of headache. Neither the spleen nor the liver was palpable and the urine contained no albumin at any time. The patient became comatose and died on the 8th day.

A specimen of liver tissue was obtained by viscerotomy after death. It was found on section to be substantially normal.

#### CASE 19—Male aged 43

General malaise abdominal pain and vomiting for 6 days. Jaundice was noticed on the 7th day and the patient came to hospital. On admission the temperature was 100 F and it rose to 102.4 before death. Jaundice was marked. There was abdominal pain and tenderness, but there was no headache. The vomiting was of bilious type and at no time contained any blood. Neither the spleen nor the liver was palpable. The urine contained no albumin at any time and the stools were clay coloured.

The patient died on the 10th day and a specimen of liver tissue was obtained after death by viscerotomy. Paraffin sections of this tissue showed no very decided abnormality. The central veins were dilated, and the columns of liver cells in the lobules separated from each other as if by fluid but not markedly so and the tissue was substantially normal.

#### CASE 5—Male aged 25

Abdominal discomfort and nausea for 3 days. Jaundice appeared on the 4th day. There was no pyrexia. The spleen and liver were both enlarged and there was some tenderness over the liver. The stools were clay coloured, and there was no albuminuria. The jaundice deepened for some days and then slowly disappeared.

#### CASE 12—Male aged 22.

Colic, diarrhoea and nausea for 7 days. Jaundice appeared on the 7th day and the patient was admitted to hospital on the 10th day. There was no pyrexia. The spleen and liver were both considerably enlarged and the latter was tender. There was no albuminuria. The stools were bulky and very pale.

The jaundice deepened for 3 or 4 days and then slowly disappeared the conjunctivae being clear by the 25th day.

### LABORATORY FINDINGS AND DIAGNOSIS

Every precaution was taken to exclude from this series cases which could possibly be ascribed to any of the known specific causes of jaundice.

Malaria and relapsing fever were excluded by repeated examinations of the blood in every case. This was of great importance in the case of the latter disease as during the period under review there were two small localized outbreaks in El Obeid. At the time of these outbreaks, not only were all proven

There are some differences between the four liver sections. Since the aetiology is unknown it cannot be stated that all our cases belong to the same nosological unit. Epidemiologically however there are reasonable grounds for this assumption. The patients all died of the same clinical entity and there is nothing in the histopathology inconsistent with the view that the lesions in the various livers should be interpreted as different stages or degrees of the same type of injury.

From the considerable degenerative changes in the parenchyma cells, it looks as if the primary factor is an acute injury to the liver cells causing necrosis. This injury appears to fall primarily or most heavily on the cells at the centre of the lobule, around the central vein. When the condition is more advanced, or more severe, practically all the cells in the lobule may be affected, only single cells, or small groups, surviving. These tend to be peripherally situated and if the patient survives may become foci of regenerating liver tissue. The necrosis is accompanied by or in the early stages immediately followed by an inflammatory infiltration. It is principally mononuclear and appears to be associated with some hypertrophy or at least increased prominence of the Kupffer cells. It is uncertain whether this infiltration represents a true hepatitis or the preliminary process of repair after a considerable necrosis of liver tissue. We would note, however, that while the necrosis appears to be primarily central in evolution, the cellular infiltration is essentially periportal. It is often assumed that the distribution in the lobule of any lesion indicates the route by which the causal agent reached the liver, a periportal distribution being produced by agents which come to the liver via the portal circulation, and a central distribution by agents which are carried in the systemic circulation. The observations here recorded suggest that the distribution depends more on the type of reaction produced than on the route by which the causal agent reaches the liver. This conclusion is in the main consistent with the findings in experimental hepatic injuries induced either on a nutritional basis, or by certain chemical poisons, such as carbon tetrachloride.

In addition to the changes described above there was in our sections a variable degree of connective tissue proliferation. This was particularly marked in the liver of Case 33, where young connective tissue was seen not only in the periportal regions but also round the central veins and extending between the islands and columns of liver cells. The condition in this instance has features of a beginning cirrhotic process. Varying degrees of connective tissue were noted in the portal regions in the other livers.

There is nothing specific or pathognomonic in this picture. The changes do not, however, suggest leptospirosis, and are quite distinct from those found in malaria, yellow fever, relapsing fever, rift valley fever, typhoid and paratyphoid infections as observed in man and animals, and from those described by ANDERSEN (1837) in the livers of swine infected experimentally from human cases of jaundice.

In general terms, the lesion may be described as a central necrosis, becoming in the more severe (or more advanced) forms an acute or subacute yellow atrophy without the proliferation of bile duct epithelium often described in this condition. A somewhat similar series of changes in the liver is recorded by Fox *et al* (1942) in the outbreak of jaundice associated with yellow fever immunization in Brazil and resemblance can be discerned between the liver lesions in kuku-ruku disease (cf HUDSON 1931) and those in some of our cases. A similar picture of central necrosis and acute yellow atrophy, or toxic cirrhosis, as MALLORY (1926) calls it can be produced by a number of chemical poisons. In epidemics of infectious (or catarrhal) jaundice it has often been noted that the rare fatal cases resemble acute yellow atrophy (COCKAYNE, 1912; BLUMER, 1923). We have studied carefully ROHOLM and IVERSEN's (1939) description based on aspiration biopsies, of the liver changes in acute epidemic hepatitis (catarrhal jaundice) in Denmark. It seems to us that the liver lesions in the present series correspond in a general way with the pathological process described by those authors although in our cases the necrotic changes are more extreme, and if our patients' histories about duration of illness can be relied on of more rapid evolution. It is possible that the extreme degree of necrosis seen in two of our cases, and the clarity of its central distribution in Case 16 were due in part to the fact that our specimens were obtained post-mortem even although they were all obtained within an hour after death. From a comparison of liver specimens obtained before and after death in a case of subacute atrophy of the liver ROHOLM and IVERSEN are of the opinion that the complete necrosis of liver parenchyma usually found postmortem in this condition is a phenomenon largely due to postmortem autolysis. Their conclusions are in agreement with EPPINGER's (1937) opinion that catarrhal jaundice is an acute yellow atrophy on a very small scale, and support the conclusion reached earlier by COCKAYNE (1912) on clinical and epidemiological grounds, that two forms of disease are due to a different course of the same pathological process.

It cannot, of course be stated that our cases have the same aetiology as cases of epidemic hepatitis and acute yellow atrophy in Europe and other parts of the world. Many toxic substances can cause similar lesions. In experimental animals similar types of hepatic injury can be induced on a nutritional basis. Describing some of the lesions thus produced in rats GYORGY and GOLDBLATT (1939) state that they resemble the changes seen in various kinds of poisoning particularly carbon tetrachloride, and bear some resemblance to the acute and subacute stages of yellow liver atrophy in man.

#### DISCUSSION

More than 10 years ago KUMM (1931) discussing the literature relating to epidemic infectious diseases associated with jaundice, concluded that the subject was in a state of confusion. It is not much clearer today except as

regards pathology VIRCHOW'S (1865) doctrinal conception of "catarrhal jaundice" as a retention icterus secondary to an unspecified duodenal catarrh blocking the bile duct has been abandoned by most workers, and few would now challenge the conclusion that the primary lesion in such cases is a hepatitis, with destruction of liver parenchyma.

The subject has been most fully studied in the Scandinavian countries. Its importance is emphasised by the wide outbreaks of jaundice which have occurred in most theatres of the present war (cf. *Journal of the American Medical Association*, 5th September 1942) and in occupied Europe (GUTZEIT 1942; DIETRICH 1942). Additional interest attaches at the present time to the outbreaks of jaundice which have occurred in Brazil (FOX *et al.* 1942) and in the United States Army (*J. Amer. med. Assoc.*, loc. cit.) after vaccination against yellow fever. Outbreaks of jaundice have also been noted in association with the use of convalescent serum in measles prophylaxis (PROPERT 1938; McNALLY 1938), while FINDLAY and MACCALLUM (1938) have recorded other instances of hepatitis and jaundice following immunization against virus diseases in man and animals. At present it cannot be stated that all those different outbreaks were due to one and the same disease. They have a number of common features, and the aetiology in all cases is unknown.

The interest of the present writers is concerned primarily with the cases of obscure jaundice in the Sudan and other parts of Africa to which attention has been attracted in recent years during attempts to identify clinical cases of yellow fever. The condition may occur sporadically but sometimes small outbreaks are observed. In individual cases the disease varies clinically from a mild indisposition to a grave illness, with deep jaundice, black vomit and rapidly fatal outcome. Cases of the latter type in which death occurs from the 5th to the 8th day may be very similar clinically to severe cases of yellow fever. On several occasions it has been possible to study individual cases or small outbreaks in the Sudan: the details have been recorded from time to time in the *Annual Reports of the Sudan Medical Service*. Recovery from this condition produces no immunity to yellow fever. The liver lesions in fatal cases are different from those of yellow fever but resemble closely the lesions described in the present paper. In no instance has *Leptospira* been found, and agglutination tests against this organism, carried out in the Wellcome Research Institution, London, with sera from recovered cases, have always been negative. In two cases observed by one of us the jaundice was associated with a *B. farci* *alkaligenes* septicæmia but otherwise all examinations of blood, faeces, and urine have been negative, and no relation to fevers of the typhoid paratyphoid group has been observed. We have tried on various occasions to transmit the disease to animals by the inoculation of blood or serum into rats, mice and rabbits (including albino varieties) guinea-pigs, monkeys, gerbilles, hedge hogs, and *Hyrax* but without success. The cause of the condition, therefore, remains obscure. Yet, if the record of viscerotome liver specimens submitted

from suspected cases of yellow fever is any indication, more people die in the Sudan of this condition than of yellow fever, the Nuba Mountains epidemic being excluded.

It cannot, of course, be stated that all such cases of obscure jaundice observed in the Sudan have a common aetiology. In many instances the only available data are an indefinite history of jaundice and a small piece of liver tissue obtained by the viscerotome. E. L. SMITH (1942) has recently published notes on fourteen cases of obscure jaundice from West Africa, in which no definite cause could be elicited. It is evident from his paper that in Africa clinical jaundice may be associated with a variety of conditions about which there is little accurate knowledge, and he suggests the possibility that certain of the native medicines in common use in Nigeria contain hepato-toxic substances. There is no indication from SMITH's paper that the cases described were in any way related to each other as in an outbreak, like the cases in the present paper. Obscure epidemics associated with jaundice have, however, been reported from the African continent by BEEUWKES *et al.* (1931) STEFANOPOULO (1933), VAN DEN BERGHE (1935) and others. In spite of the fact that no causal agent could be discovered, certain of these outbreaks have been regarded as new and specific diseases.

WHITMAN (1924) produced fatal jaundice in two out of three rabbits inoculated from human cases during an outbreak of jaundice at the Ohio State Penitentiary and ANDERSEN (1937) records the transmission of epidemic jaundice to swine. Most other workers who have studied cases or epidemics of jaundice for which there was no discoverable cause have failed, as have the present writers to transmit the disease to animals. Nevertheless, there is circumstantial evidence that certain forms of epidemic jaundice are caused by a filtrable virus (FINDLAY *et al.* 1931). The movement of catarrhal jaundice epidemics from place to place in England is consistent with this view. The circumstances relating to the occurrence of outbreaks of jaundice after yellow fever vaccination, and the use of convalescent serum in measles all point to a filtrable virus. FINDLAY and MACCALLUM (1938) have indeed suggested that these accidents were due to the presence as a contaminant, of the virus of common infective hepatitis or catarrhal jaundice.

The possibility of a double aetiology in epidemic jaundice has been suggested by various workers (FOX *et al.*, 1942). Over twenty years ago DAVIS and WHIPPLE (1919) showed that the destructive action of chloroform on the liver was intensified by previously withholding food or by a high fat diet. MINOT (1926) showed that carbon tetrachloride necrosis in dogs occurred only in animals on a calcium-poor diet. In recent years several papers have appeared recording production of hepatic injury on a nutritional basis in experimental animals. EARLE *et al.* (1942) have shown that excess dietary cystine causes hepatic injury in rats, and that this can be modified by diet, but is not prevented by choline. GYORGY and GOLDBLATT (1942) produced hepatic injury also in



rats, by a low protein high fat diet the addition of a small quantity of cystine increased the severity of the liver damage, while choline prevented it. Although the dietary factors instrumental in the pathogenesis of the liver damage require further elucidation, the lesions produced are very definite. Animals with dietary hepatic injury exhibit, in sequence, changes varying from diffuse necrosis, resembling human acute or subacute yellow atrophy to advanced portal cirrhosis. From the point of general pathology it is of great interest that identical aetiological conditions may lead, in rats, either to necrosis or to cirrhosis of the liver or to both (GYONGY and GOLDBLATT 1942). If it can be shown that these conclusions apply also to the human subject, previous ideas on the pathology of the liver will have to be amplified. With regard to the cases in the present paper we have no accurate information on the dietetic history to offer. Inquiries revealed no apparent differences between individuals who got jaundice, and others who did not. Most of the inhabitants of the area live on a diet characterized by extreme monotony low caloric value, and deficiency of animal protein. According to CORKILL (1939) there is an apparent absence of vitamins A, B<sub>1</sub>, and C from the diet of most tribal Sudanese for 4 to 6 months a year a state of affairs mainly due to seasonal desiccation. With regard to calcium deficiency or the possible existence of chronic intoxications like selenium poisoning nothing is known.

In addition to jaundice, hepatic cirrhosis of unknown origin is very frequently encountered in the Sudan. Primary carcinoma of the liver especially that form which arises in relation to cirrhosis is also encountered frequently although carcinoma of the alimentary tract—excluding squamous epithelioma of the mouth and anus—is not often seen (cf. *Annual Reports of the Sudan Medical Service* 1935 to 1942). Similar observations have been reported from other African territories (SMITH and ELMES, 1934; BERMAN 1941). The relationship between acute and subacute yellow atrophy nodular hyperplasia, cirrhosis, and primary carcinoma of the liver was pointed out many years ago by MUIR (1906), but the reasons why these conditions should be so prevalent among Africans are obscure. The possibility that there might be some relation between the obscure jaundice so often seen in the Sudan and cirrhosis was suggested to us by BERGSTRAND's (1930) monograph, a copy of which was shown to one of us by Brig G. M. FINDLAY. Before BERGSTRAND's paper appeared EHRLSTROM (1927) another Scandinavian worker coined the term "hepatitis endemica" to include extrahepatic jaundice, acute yellow atrophy and what he called chronic hepatitis, the latter being reminiscent of a condition, or series of conditions, frequently seen clinically in the Sudan. The view that agents which cause hepatic necrosis may under different circumstances, produce cirrhosis is in accordance with modern pathology. MUIR (1906) states that "in fact, acute and subacute yellow atrophy nodular hyperplasia and cirrhosis form a series of changes differing in extent and rapidity rather than in nature

The subject is one of great difficulty and while the relation of cirrhosis to primary hepatic carcinoma is clear histologically in many cases, we have been unable to demonstrate any clear correlation between cirrhosis and epidemic or sporadic jaundice in the Sudan. Viscerotomy liver specimens are seen from time to time in which cirrhotic changes of varying degree occur side by side with the more acute changes commonly seen in cases of obscure jaundice. The possibility always exists that in such cases the acute condition is merely superimposed by accident on a previously cirrhotic liver, and a further source of confusion is the differentiation between true cirrhosis and multiple nodular hyperplasia. Occasionally we have obtained a history of past jaundice in advanced cases of cirrhosis this is likewise of little significance unless the factor of coincidence can be excluded.

## REFERENCES

- ANDERSEN T THUNE. (1937) *Acta med scand* 93 209 Cited by ROHOLM & IVERSEN (1939)
- BEEUWCKES H WALCOTT A M & KUMM, H. W. (1931) *Trans R. Soc trop Med Hyg* 24 429
- BERGSTRAND H (1930) *Über die Akute und Chronische gelbe Leberatrophie* Leipzig Georg Thieme
- BERMAN C (1941) *S Afr J med Sci* 6 145
- BLUMER G (1923) *J Amer med Ass* 81 353
- COCKAYNE, E. A. (1912) *Quart J Med* 6 1
- CORKILL, N. L. (1939). *Lancet* 1 1203
- DAVIS, N. C. & WHIPPLE, G. H. (1919) *Arch intern Med* 23 612
- DIETRICH, S. (1942) Reviewed in *Bull. War Med* 3 29
- EARLE, D. P. & VICTOR, J. (1942) *J exp Med* 76 179
- EHRSTRÖM, R. (1927) *Acta med scand*, 65 179
- EPPINGER, H. (1937) *Die Leberkrankheiten* Berlin Springer Cited by ROHOLM & IVERSEN (1939)
- FINDLAY G M DUNLOP J L. & BROWN H C. (1931) *Trans R. Soc trop Med Hyg* 26 7
- & MACCALLUM F O. (1938) *Proc R. Soc Med* 31 799
- KIRK R & MACCALLUM F O. (1941) *Ann trop Med Parasit* 35 121
- & LEWIS D J. (1941) *Ibid* 35 149
- FOX, J. P. MANGA, C. PIENNA, H. A. & PARA M. (1942) *Amer J Hyg* 36 68
- GEORGY P & GOLDBLATT H. (1939) *J exp Med* 70 185
- (1942) *Ibid* 75 353
- GUTZERT H. (1942) Reviewed in *Bull War Med* 3 30
- HORGAN E S. (1943) *Ann Rep Sudan Med Serv for 1941* (In the press)
- HUDSON N P. (1931) *Trans R. Soc trop Med Hyg* 26 453
- J Amer med Ass* (1942) Editorial 120 51
- KIRK R. (1933) *Trans R. Soc trop Med Hyg* 21 667
- (1941) *Ann trop Med Parasit* 35 67
- KUMM, H. W. (1931) *Trans R. Soc trop Med Hyg* 24 421
- MALLORY F B. (1926) *Arch intern Med* cited by HUDSON (1931)
- MCCALTY A. S. (1938) *Rep med Offr Minist Hth Lond* 1937
- MENOT A. S. (1929) *Proc Soc exp Biol NY* 24 617
- MUIR, R. (1908) *J Path Bact* 13 287
- (1936) *Text Book of Pathology* p 603 4th Ed London Arnold & Co

- PROBERT S. A. (1933) *Brit Med J.*, 2, 6—
- ROEHLI, K. & IVERSEN, P. (1939) *Acta path. microbiol. scand.* 16 47
- SMITH, E. L. (1947) *Ann. trop. Med. Parasit.*, 38 33.
- SMITH, E. C. & ELMS, B. G. T. (1934) *Ibid.*, 28 491
- STEFANOPOLLO, G. (1933) *Bull. Soc. Path. exot.*, 28 380
- SUDAN MEDICAL SERVICE *Annual Reports (1935-1947)* Khartoum McCorquodale & Co.
- VAN DEN BERGHE, L. (1935) *Ann. Soc. belge Med. trop.* 15 561
- WHITMAN, W. A. (1924) *Ohio State med. J.*, 20, 273.

## THE CAUSATION OF TROPICAL ULCER.

BY

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*Ulcus tropicum* is not only a source of great debility and incapacity from work throughout the tropics but is also at times a serious danger to the life or limb of the patient. Twelve years ago two patients were admitted to a C.M.S. Hospital in Uganda. They were father and son. The father was suffering from a tropical ulcer which had involved and divided his tibia, while the son had an ulcer extending from knee to ankle. Both cases required amputation to save their lives.

The disease was a serious affliction amongst carriers to the East African Force during the war 1914-18. It is of special interest to us in this area at the present time on account of its high incidence amongst local troops.

Much literature has been written on its aetiology. PROVAZEK attributed the disease to *Spirochaeta schaudinni*. Many writers have noted the presence of spirochaetes and fusiform bacilli, one authority (*War Office Memoranda* 1941) even claiming that a diagnosis can be made by the discovery of these

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I wish to record my gratitude to Lt.-Col. J. W. WALKER, O.C. 8th (E.A.) Field Ambulance for his permission and encouragement, to Capt. A. P. CURRAN and Capt. R. M. CADENHEAD medical officers to the Somali battalions for their co-operation and to Sgt. W. G. FLEBY for his supervision of the treatments.

organisms in a stained smear from an ulcer. Some on the other hand, such as ROY believe a diplococcus to be the causal organism. They maintain that, whereas spirochaetes and fusiform bacilli cannot always be found, the diplococcus is invariably present. LLOYD PATTERSON succeeded in the direct transmission of a typical sore to an abraded surface. Some investigators have observed an association with chronic malaria, while others blame malnutrition debility and dietary deficiencies. LOEWENTHAL, working in Uganda, was of the opinion that the disease occurred more frequently in natives on a low calcium diet, and claimed excellent results from the intravenous injection of calcium chloride. SCOTT (1941) noted a deficiency of vitamin A in the mine and estate diets in Tanganyika, where the incidence of tropical ulcers is high. CLEMENTS in Melanesia, and JAMES in the Solomon Islands (*Manson's Tropical Diseases* 1941), blamed a combination of diet deficiencies (especially B), debility and climatic factors. As Sir LEONARD ROGERS (1942) states 'Its aetiology is still unsettled'. There is, however a good deal of evidence in favour of a dietary deficiency. During the years 1929-31 the writer saw hundreds of cases of tropical ulcer at Ngara in the Teso district of Uganda, a hot, infertile, thickly populated country inhabited by people who were for the most part thin and undernourished. Major A McDOWELL DAVIES, in a personal communication concerning tropical ulcers in Somali civilians, stated that whereas he often observed cases of the disease among such persons as cripples, orphans and old people who could not earn sufficient money to receive an adequate diet, he did not see it in the agricultural community or in better off Somalis possessing agricultural interests.

On turning to the condition as it affects our troops in this area, one cannot help being impressed by the extraordinary distribution of the disease. Out of a total of 570 East Africans admitted to 8th (E.A.) Field Ambulance during the period of 6 months, 20th November 1942, to 20th May 1943 only one case was labelled with a diagnosis of *ulcus tropicum* (and it is doubtful whether even this patient's persistent sore on the shin was not actually caused by the presence of a layer of necrotic tibial bone rather than by a true tropical ulcer). On the other hand, out of 292 Somali soldiers admitted during the same period, no less than 143 were affected with sloughing phagedaena. Converting these figures to percentages we find that 49 per cent. of the Somali admissions were suffering from tropical ulcer as opposed to under 0.2 per cent. of the East Africans. What is the cause of this remarkable limitation of the disease to Somali troops? The Somalis and East Africans are living under identical climatic and other conditions, with one exception. They differ in their diet. A comparison of the two diets is tabulated below (Table I).

The main difference is that, whereas Somalis receive rations of jowari and rice, East Africans are supplied with maize meal. Moreover although both troops are provided with ghee substitute and dried beans, while the East Africans consume and enjoy these foods the Somalis dislike and refuse them. In order to confirm, if possible, the suspicion that the dietary difference was the cause

of the peculiar distribution of the disease, six Somalis with tropical ulcers were admitted to an East African ward where they were given the ordinary East African diet. The only local treatment was a dry dressing twice a day. All cases quickly improved in spite of the fact that two of the patients on admission were suffering from severe ulcers of the rapidly spreading variety. Also in support of this theory was the instance of three local Abyssinian natives with typical tropical ulcers who were working as personal servants amongst East Africans in East African units. On being questioned as to their food, they stated that they did not eat the maize meal beans and ghee substitute consumed by their companions: they took rice, bananas and ordinary ghee instead.

It may be argued that Somalis may be racially or for some other reason, unduly susceptible to tropical ulcers, but against this view is the interesting fact that amongst the personnel of another unit in this area are 120 Somali drivers, several of whom have been treated as out patients for skin abrasions of the lower part of the leg, not a single case of tropical ulcer has occurred in this unit. It is significant that these Somalis have been persuaded to eat all the ordinary East African rations, except maize meal. The possibility presented itself that there might be some essential substance in beans or ghee substitute which was protecting the Somalis of this unit and the East African troops against the disease.

The diet of the Somali battalions is outlined in Table II (see pages 208 and 209).

Beans and ghee substitute, which were also supplied, have been omitted from the list because, as already explained they are unacceptable to the Somalis and persistently declined. If we analyse this diet we find that, whereas there are adequate allowances of protein, phosphorus, iron, calories, vitamin B<sub>1</sub> and vitamin C there is a shortage of three essentials. The deficient substances are calcium, vitamin A and riboflavin which fall short of the minimum needs of 0.6 gramme, 5 000 international units and 3 mg. by 0.34 gramme, 4 077 international units and 2.46 mg. respectively. There is considerable difference of opinion regarding the physiological requirement of vitamin A, AYKROYD (1937) suggesting a minimum of 3 000 international units, and ROSE (1933) an intake of 140 international units per 100 calories (LEONG 1939). There can, however, be little doubt that the figure of 923 international units for the Somali troops is insufficient. The nicotinic acid value for the diet is approximately 17 mg. The protective level of this vitamin has apparently not been accurately estimated because as pointed out by LEONG (1940) the relationship between diet and pellagra cannot be explained in terms of the nicotinic acid content of the diet alone. (The nicotinic acid content, 15 mg. of the typical maize diet in Rumania, where the incidence of pellagra is high is greater than that of the Asiatics in Malaya, 10 mg. and India, 5 to 11 mg. where pellagra is rare.)

It must be pointed out that the deficits in the Somali food are due, not to any error in the official diet, but to the peculiar idiosyncrasy of Somalis in rejecting foods which are accepted by East Africans.

TABLE  
COMPARISON OF EAST AFRICAN

Foodstuff	Amount per Day Ounces	Protein. Grammes	Fat Grammes	Carbo- hydrate. Grammes	Calcium. Grammes	Phos- phorus Grammes	Iron Mg
SUPPLEMENTARY							
Maize meal (white)	22	70.4	24.2	466.4	0.044	1.553 <sup>a</sup>	2.
Beans	4	24.4	—	81.6	0.204	0.415 <sup>a</sup>	7.6
Ghee substitute ...	1	—	22.4 <sup>a</sup>	—	—	—	—
Total .. ..		94.8	5.6	518	0.248	1.968	29.6
SUPPLEMENTARY							
Jowar <sup>b</sup>	16	47	8.6	336	0.136	1.27	28.1
Rice	6	11.4	1.8	157.6	0.006	0.163 <sup>a</sup>	0.6
Total		58.4	10.4	493.6	0.142	1.433	28.7
BALANCE IN FAVOUR							
		36.4	42.2	24.4	0.106	0.563	0.9
BALANCE IN FAVOUR							
		—	—	—	—	—	—

TABLE  
SOMALI

Foodstuff	Amount per Day Ounces	Protein. Grammes	Fat Grammes	Carbo- hydrate Grammes	Calcium Grammes	Phos- phorus Grammes	Iron Mg.
Rice	6	11.4	1.8	157.6	0.006	0.163 <sup>a</sup>	0.6
Jowar	16	47.0	8.6	336	0.136	1.27	28.1
Fresh beef	8	46.4	16.8	—	0.016	0.00 <sup>a</sup>	8.0
Cabbage	4	4	—	8	0.060	0.033 <sup>a</sup>	0.8
Orange	1 (about 3½)	0.7	—	8.4	0.042	0.02 <sup>a</sup>	0.35
Sugar	2	—	—	86.8	—	—	—
Salt	½	—	—	—	—	—	—
Tea	½	—	—	—	—	—	—
Total		107.9	27	566.8	0.22	1.746	37.85
Minimum require- ment		About 80	—	—	0.6 <sup>c</sup>	1	10 <sup>22</sup>
Deficit		Nd	—	—	0.34	Nd	Nd

## NOTES ON TABLE II

1. *Rice*—The amount of pericarp which was found to be 28 per cent., was determined by VIDON and rice, the ascorbic (1840) and nicotinic acid (LIXON, 1940) contents were estimated. VIDON and FILICIAHO's examination of each grain for the amount of pericarp remaining, which is expressed as a percentage. 2. *All Cabbage*—The phosphorus value is the estimate for vegetables in the ration scale of the East Africa Command who gave no specific figure for orange. 3. *Minimum requirement of Vitamin B<sub>1</sub>*—The figure has been drawn of 10 international units per 100 calories seemed to be desirable.

I  
AND SOMALI DIETS

Calories.	Vitamin A International Units.			Vitamin B <sub>1</sub> International Units.	Riboflavin. Mg	Nicotinic Acid Mg	Vitamin C. Mg	Vitamin D International Units
	Caro- tene.	Vitamin A.	Total Vitamin A Potency					
EAST AFRICAN ITEMS.								
2,090	—	—	—	198	0.22	4.4	—	—
312	164	—	164	116	1.0	0.34 <sup>7</sup>	—	—
264 <sup>8</sup>	3,600	—	3,600 <sup>8</sup>	—	—	—	—	—
2,666	3,664	—	3,664	314	1.82	4.74	—	—
SOMALI ITEMS.								
1,611	617.4	—	617.4	340.5	Poor	Poor	—	—
672	—	—	—	63.75	0.18	4.057	—	—
2,283	617.4	—	617.4	404.25	0.18	4.057	—	—
OF EAST AFRICANS.								
383	3,046.6	—	3,046.6	—	1.64	0.693	—	—
OF SOMALIS.								
—	—	—	—	90	—	—	—	—

II  
DIET

Calories.	Vitamin A International Units.			Vitamin B <sub>1</sub> International Units.	Riboflavin. Mg	Nicotinic Acid. Mg	Vitamin C. Mg	Vitamin D International Units.
	Caro- tene.	Vitamin A.	Total Vitamin A Potency					
672	—	—	—	63.75	0.18	4.057	—	—
1,611	617.4	—	617.4	340.5	Poor	Poor	—	—
344	—	112	112	78	0.32	12	—	—
36	120	—	120	21	0.04	0.456 <sup>7</sup>	45	—
38.5	73.5	—	73.5	28	—	0.316 <sup>7</sup>	49	—
232	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—
2,933	810.9	112	922.9	531.25	0.54	16.888	94	—
—	—	—	8,000 <sup>11</sup>	293.3	3 <sup>12</sup>	—	26 <sup>11</sup>	200 <sup>11</sup>
—	—	—	4,077	Nil	2.46	—	Nil	260

FELICIANO's method (19<sup>45</sup>). By applying this degree of polishing to standard figures for polished and unpolished method consists in staining 100 grams of rice with Gram's iodine for one minute followed after rinsing by the other figures except those with reference numbers, were taken from the War Office List of Food Values 3 4. Orange — The stated quantity of nicotinic acid is based on the average for the fruits examined by Larnier from a report of the Technical Commission of the League of Nations 1919 which stated that an



It was decided to give therapeutic tests with the deficient substances, namely calcium, vitamin A and riboflavin, in the hope of obtaining information about the cause of tropical ulcers, just as one sometimes employs a therapeutic test of quinine to clinch a diagnosis of malaria, or of N.A.B. for syphilis. Nicotinic acid was included amongst the tests, partly because LEONG'S estimate (1940) for this substance in 8 ounces of beef (boiled for 20 minutes) after deducting 22 per cent. for waste material, is only 4.25 mg. (one third of the War Office figure), and partly because the bacteriology of *ulcus tropicum* is so similar to that of Vincent's angina, to which a deficiency of nicotinic acid predisposes. Tests were also made with ascorbic acid under the (probably mistaken) impression that there might be a shortage of vitamin C in the diet partly on account of the African's habit of cooking his cabbage (and in fact, all his food) for several hours before consumption, and partly because there seemed to have been a shortage of oranges in the Somali battalions for a few weeks.

The patients were divided into six batches, and the therapeutic tests were administered as follows: calcium was given in a daily dose of 0.5 gramme, at first intramuscularly as calcium gluconate and later when the supply of this preparation had become exhausted as calcium chloride intravenously. 1 gramme of the latter salt was given to severe cases. Vitamin A was supplied in the form of cod liver oil  $\frac{1}{2}$  ounce three times a day. One and a half ounces of cod liver oil contain 25,200 international units of vitamin A, according to the B.P. standard of 600 international units per gramme. LEVO'S analysis (1939) of cod liver oil varied from 200 to 800 international units per gramme. (It is interesting to note that, just as dairy products have a seasonal variation in vitamin A content according to the amount of carotene absorbed by the different animals, so the vitamin A concentration of cod liver oil is modified by climate. Newfoundland and British cod liver oil contain considerably more vitamin A than that of the cod caught in Norwegian waters (LEITCH 1930) the concentration presumably being proportional to the amount of carotene present in the local marine plants which form the ultimate source of the vitamin A in these fish oils.) A daily ration of 7 ounces of condensed milk was prescribed as a test for riboflavin. As no nicotinic acid was available, coramine, being the diethylamide of nicotinic acid, was injected in a dose of 3-4 c.c. intramuscularly per day. Vitamin C was administered as ascorbic acid, one tablet of 25 mg. three times a day. Five cases were chosen as controls and were given no specific treatment at all. All these patients were provided with the Somali diet as outlined above, were accommodated in special sick quarters apart from the East African patients and were supplied with a separate kitchen and Somali cook. The only local treatment was a dry dressing twice a day which obviated any possible confusion with benefit from some antiseptic application. All cases were measured every 3 days. Major A. McDOWELL DAVIES kindly designed an ingenious machine for the accurate measurement of the circumference of the ulcers. This instrument, which was constructed out of a carefully graduated

disc fixed by a rivet to a metal handle, could be properly used  
of the ulcer and was thus able to take into account ~~the~~  
Examinations with this appliance were carried out in con-  
tions of width.

Cases are not cited as improvements unless they show appearance of healthy granulations and signs of ~~epithelization~~ actual diminution in size of the ulcers within the first 5 ~~days~~ commencement of treatment.

Let us now examine the results of these tests. The results are described because they so to speak, put a check on our other findings. Sixty per cent. showed improvement. This is a high figure, but it should be pointed out that, although the patients were chosen at random serious cases were for humanitarian reasons chosen as controls and given treatment which appeared to offer some benefit to them. If we include amongst the controls the ten patients who were given ascorbic acid, which proved to be of no therapeutic value, the figure of 40 per cent. which is probably a more accurate estimate of cases liable to spontaneous cure on rest in bed and dry food is tabulated below —

Treatment.	Number of Improvements.	Number of Cases Treated.	Percentage of Improvements.
Controls	3	5	60%
Calcium	8	8	100%
OL morrhuae	20	27	74%
Milk	5	5	100%
Conamine	2	5	40%
Ascorbic acid	1	5	20%

Two of the ulcers, which had failed to make any progress benefited by calcium and cod liver oil respectively. The other two received no advantage from coramine, cleared up only slightly.

It is probable that the curative action of milk flavin, but from its calcium content (0.57 grams milk, or vitamin A 1540 international units. *War* for in order to settle this point, one patient was 2 c.c. intramuscularly per day which, being a liver be rich in riboflavin the case, so far from response further batch of eleven patients were provided with

in the official Somali diet, which is listed below. The pepper may be sprinkled over the food after cooking.

TABLE III  
OFFICIAL SOMALI DIET SCALE

Commodity	Daily Scale in ounces	Commodity	Daily Scale in ounces
Jowan flour or Maize meal	16 10	Dates (pitted) or Fresh vegetable	4 4
Rice	6	Orange or Sweet pepper (Peprica) or Ascorbic acid tablet	1 1 1
Fresh meat or Preserved meat	8 6	Sugar or Jaggery	
Ghee substitute			
Salt	1		
Ground nuts or Dried beans or Dried peas	4 4 4	Tea or Coffee	1 1

Another local foodstuff which has a high carotene content is the chilli (LEONG, 1939), which contains 2,268 international units per ounce of green chilli, but only 128 i.u. per ounce of red chilli. Alternative supplies of the vitamin might be obtained from lettuce, watercress, or spinach, which contain 7,068, 6,156 and 9,120 i.u. per 4 oz. respectively (These are LEONG's figures. The War Office estimate for spinach is only 4,920 international units. As the vitamin content of foodstuffs varies greatly according to different observers, figures which are not worked out on the spot can only serve as a rough guide.)

Protection of the feet and legs by boots and puttees has been recommended in order to avoid the minor abrasion which usually precedes the ulcer. This measure is undoubtedly of value, but the importance of the initial trauma as an aetiological factor must not be exaggerated. Capt. H. M. FRYE, R.A.M.C., Medical Officer to an East African unit (7th Battalion King's African Rifles), in a personal communication, stated that for a space of 6 weeks the footwear of the men in his battalion consisted only of sandals with no socks. During this period, although there was a high percentage of scratches and foot injuries, there was not a single case of tropical ulcer.

## SUMMARY

1 Tropical ulcer was confined to two Somali battalions, whose food differed from that of the East Africans. The main dissimilarity between the two diets was a deficiency of vitamin A and riboflavin in that of the Somalis.

2. The disease did not attack Somalis of another unit whose food included beans and ghee substitute. The latter substance contains 3,500 international units of vitamin A per ounce.

3 Abyssinians in East African units who refused the East African rations developed typical tropical ulcers.

4 Tests on 135 patients have been described and suggest that vitamin A deficiency is the cause, or a major factor in the aetiology of tropical ulcer.

5 Prophylactic measures, based on this theory consist in the administration of a carotene-rich substance such as Abyssinian sweet pepper, green chillies, or lettuce.

## REFERENCES

- Appendix to Medical Routine Orders East Africa Command* (1941) No 32  
 ATKROYD W. R. (1937) *Indian Health Bulletin* No 23  
*Field Service Hygiene Notes India* (1940) p 337  
 LEITCH J. N. (1930) *Dietetics in Warm Climates* p 358 London Harrison & Sons  
 LEONG P. C. (1939) *J. Malaya Br Brit med Ass* 2 219  
 ——— (1940) *Ibid* 4 261  
*List of Food Values in Ration Scale of East Africa Command.*  
 MANSON BAKER P. H. (1941) *Manson's Tropical Diseases* p 674 London Cassell & Co.  
 MOTTAM V. H. (1937) *Practitioner* 139 71  
 ROGERS L. (1942) *Tropical Medicine* p 348 London J & A Churchill.  
 ROTHLEN E. (1940) *Schweiz med Wschr* 27 641 Quoted by *Bull. War Med* (1941) 8, 185  
 SCOTT R. R. (1941) *Tanganyika Government Medical Pamphlet* No 29 p 5  
 SEBRILL, W. H. (Jnr), BUTLER, R. E., WOOLEY J. G. & ISKELL, H. (1941) *Publ Hlth Rep Wash* 58 510  
 VEDDER & FELICIANO (1928) *Philipp J Sci.* 35 351 Quoted by LEITCH, J. N. (1930) *Dietetics in Warm Climates* p 258 London Harrison & Sons  
*War Office List of Food Values*  
*War Office Memoranda on Medical Disease in Tropical and Sub-tropical Areas* (1941) p 210



## FOOT LESIONS IN AFRICANS

BY

M J G FURNELL, M.R.C.S. L.R.C.P CAPT R.A.M.C.\*

Comparatively little attention has been paid in textbooks of tropical medicine to minor lesions of the feet in the inhabitants of tropical countries. Such minor lesions, however, impair the physical efficiency of very large numbers, more especially in a hot moist climate such as that of West Africa.

For a time it was the policy in obtaining recruits for the armed forces in West Africa to reject all those who were supposed to be suffering from yaws of the feet, although, as there was considerable uncertainty as to what constituted yaws of the feet, it became the practice more especially among newly arrived medical officers to reject as unfit for military service all men suffering from lesions of the soles of the feet.

In view of the loss of man power thus involved it was decided to attempt a classification of the lesions found in the feet so that conclusions could be reached in regard to their aetiology and prevention.

Investigations were carried out in a static unit composed mainly of Gold Coast Africans with a sprinkling of Nigerians. About half the Gold Coast Africans came from the Northern Territories.

### TYPES OF LESIONS.

The lesions commonly seen in the feet of Africans are provisionally classified as follows —

#### 1 *Cracked soles*

These lesions are characterized by long cracks, sometimes forked at an acute angle with the skin. The condition may or may not be associated with a general hyperkeratinization and with cracking of the heels. The condition is relatively painless. It occurs most frequently among the Northern Territory men who live in dry savannah country. This suggests that it is caused by excessive drying combined with trauma from small particles of sand. (Fig 1)

\* The author would like to express his thanks to Brigadier G. M. FINDLAY, Consultant Physician in Tropical Medicine to West Africa, without whose advice and encouragement this article would not have been written.

## 2. *Pitting of the thick skin of the sole*

This condition appears to be identical with what CASTELLANI terms "*kernoma plantare sulcatum*" though the essential lesion appears to be an excavation of the skin rather than a keratoma. It may occur in the same foot as cracked soles, in which case the pitting usually occurs in the transverse metatarsal line and the cracks on the heels.

The lesion itself is composed of small round holes in the skin that tend to coalesce to form lines and are like, and in fact are sometimes simulated by small holes dug out with the point of a penknife. This is a favourite form of malingering and one which should always be kept in mind.

It appears that this condition is due to minor trauma as by gravel on concrete floors, following softening by prolonged and frequent immersion in water. It was found to be common in the wetter areas such as the Enchi district of the Western Province of the Gold Coast. The fact that it may occur in the same foot as cracks due to dryness may be explained by the fact that the ground even in the Northern Territories, is waterlogged during the rainy season and also that the Northern Territory men have to pass through the forest country on their way to the coast. The writer caused typical pitting of the skin on the metatarsal arches of his own feet by going shooting for a week in mangrove swamps for some four hours daily when, clad only in gymnasium shoes. (Fig. 2.)

## 3. *Corns (verruca plantaris)*

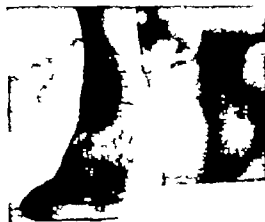
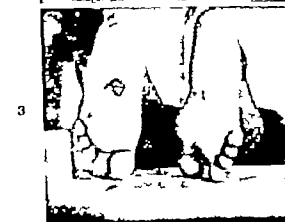
This is the only really painful condition met with in this series. The lesions occur on the weight bearing sole and are composed of a thickened ring of keratin surrounding a soft inner core. Pressure on the core itself or squeezing causes exquisite pain. The condition strongly resembles verruca plantaris, but, as laboratory facilities were not available, a definite diagnosis could not be made. (Fig. 3.)

## 4. *Rat-bites*

This condition, which was seen on four occasions, is due to the bites of *Rattus rattus* which feeds on the thickened keratin of the sole while the victim is asleep. The appearance is very similar to that of mouse-nibbled cheese and once seen and recognized, is unlikely to be mistaken for anything else. If unrecognized the man may be wrongly accused of having a self inflicted injury (Fig. 4.)

## 5. *Disease of the skin of the instep*

Two cases were seen in which there was a scaly condition of the non weight bearing skin of the instep. In both cases the skin was at first soft, crumbling and tender but later it became hard, pigmented and painless. The aetiology of this condition is unknown but it may possibly be a fungoid infection. (Fig. 5.)



#### DESCRIPTION OF FIGURES

FIG. 1 —Cracked soles

FIG. 2 —Pitting of the soles

FIG. 3 —A plantar corn (possibly verruca plantaris) the black colour is due to previous application of tar

FIG. 4 —A rat bite of the heel

FIG. 5 — Cut-onion effect with a scaly condition of the skin of the instep





## 6 'Cut onion' effect

This condition is so common as to be nearly within the bounds of normal. It is a round area with concentric circles of exposed layers of the epidermis producing the 'cut-onion' appearance. It is caused by the grinding of the foot, particularly of the heel where the lesion is most frequently seen into the latente of the parade ground during foot drill.

## 7 Other lesions of the feet

Sepsis, secondary to either minor trauma or to guinea worm infection and blisters, which are surprisingly common and are frequently multiple, caused more loss of man-power in the unit under consideration than all the conditions mentioned above put together.

## AETIOLOGY

Evidence of the aetiology of certain of the lesions described has already been brought forward.

The question of how far yaws is a causative factor is still uncertain. At first it was thought that the Kahn test might help in deciding which lesions, if any were due to yaws but after twenty-three tests had been carried out on patients with yaws of the feet the tests were abandoned as the results bore no relation to the type or severity of the lesions.

The results of the twenty three tests were as follows —

Negative 10 Positive + 4 + ± 1 +++ 8.

They did not differ from those obtained from a sample of the population with no 'yaws' of the feet.

Enlargement of the epitrochlear lymph nodes has sometimes been regarded as a sign of yaws it may however occur in syphilis, filariasis and leprosy. An examination of 125 recruits for correlation between enlarged epitrochlear lymph nodes and foot lesions gave the following results —

84 Normal feet	
Number with enlarged epitrochlear lymph nodes	62
Number with no enlarged epitrochlear lymph nodes	22
41 Diseased feet	
Number with enlarged epitrochlear lymph nodes	34
Number with no enlarged epitrochlear lymph nodes	7

It was noticeable that in the troops investigated not a single case of any of the lesions described above were seen in Africans who habitually wore sandals.

## Treatment

Treatment was at first attempted with a course of four weekly injections of 0.45, 0.6, 0.6, 0.6 grammes neoarsphenamine combined with 0.2 grammes

sobits. Permission was also given to the men to buy and wear sandals. While results with the anti yaws treatment were very disappointing it was noticed that those who wore sandals were more rapidly healed than the others.

In over 100 cases of foot lesions seen there was only one that required admission to hospital and apart from the cases with corns only two others had to be given light duty. If too much sympathy is displayed by the medical officer the numbers with foot lesions at sick parade will be greatly increased.

### *Prevention.*

It is considered that sandals form an ideal prophylactic measure both for these conditions mentioned and for minor trauma which is common and causes loss of man-power.

Sandals are considered superior to boots for the reason that they are light and allow free circulation of air thus preventing the collection of moisture within the enclosed boot. Much of the West African soldier's drill is done barefoot and the use of sandals would prevent minor trauma. On the other hand the disadvantage of sandals is that they do not give complete protection against snake-bites, jiggers or leeches and trauma in the field. Snake-bites are, however, rare in West Africa and the protection against jiggers would be nearly complete with sandals.

As deficiency in the vitamin B complex is not uncommon in African recruits the possible relation between hyperkeratosis and avitaminosis requires investigation. Care should be taken to prevent rats from biting the foot while the victim is asleep.

### CONCLUSION

1 The importance of defining the actual foot lesions which will or will not be accepted for military service is stressed.

2 Doubt is cast on the importance of yaws in the aetiology of foot lesions in Africans.

3 An account of the foot lesions found in a unit is given and some evidence of aetiology is brought forward.

4 The importance of the wearing of sandals both in treatment and in prophylaxis is emphasized.

## AN UNUSUAL CASE OF QUININE IDIOSYNCRASY

BY

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M P a grocer, aged 47 years, entered the hospital under the care of Dr M RACHMILEWITZ, on the 7th March 1942, with a history of recurrent attacks of fever preceded by chills and pain in the upper part of the abdomen.

His family history revealed that his father and one sister had died from pulmonary tuberculosis. The mother had died from cancer of the stomach. Two of his children had suffered from severe attacks of urticaria.

He was born in Poland and came to Palestine 6 years ago. He had never lived in a region known to be infested with malaria.

His past history was irrelevant except for tonsilectomy in 1934 and in the same year diarrhoea of unknown origin lasting for 1 week which subsided without any treatment.

In February 1941 he had an annoying headache and bought a powder from a pharmacist to relieve the pain. Several hours later he had a rigor with a rise in temperature to  $39.8^{\circ}\text{C}$  which lasted a few hours subsequently he felt quite well.

In April, 1941 he had a second attack similar to the first but he did not remember whether he had taken an analgetic. Some months later after taking a powder which was bought at the same pharmacy to relieve a headache, a rigor and rise of temperature followed. This time a physician was called and he suspected an attack of malaria. Though blood-examination showed no parasites, the patient was given an intramuscular injection of quinine half an hour later a second rigor with a further rise of temperature up to 40.4 C set in. The attack was accompanied by vomiting and severe pain in the epigastric region which irradiated to the right hypochondrium and the right shoulder. To combat this pain 5 c.c. of novalgin were injected. Two hours later all the symptoms disappeared and on the next day the patient felt quite well. Another physician was called, and a thorough general examination, including X ray pictures of the kidneys for paranephritic abscess and of the teeth (granuloma?) showed no pathological findings.

In December 1941 the patient began to suffer from diarrhoea. The stool examination revealed vegetative forms of *Entamoeba histolytica*. Treatment with emetin hydrochloride and stovarsol was given, after which the patient felt well, except for slight weakness which persisted from the onset of the dysentery.

In February 1942, the patient once more had an attack of pain in the right upper abdomen accompanied by rigor and hyperpyrexia. Again no malaria parasites were detected in the blood. Notwithstanding this negative finding the attending physician prescribed treatment with plasmoquine compound which contains 0.1 gramme quinine and 0.01 gramme plasmoquine. This medication had to be stopped after the second tablet, because the ingestion of each tablet was followed by a severe rigor and rise of temperature.

On admission to hospital there were no special findings except for tenderness of the right hypochondrium and a hypersensitive zone over the liver.

#### Laboratory Findings

Blood-count red blood cells, 4,080,000 Hb 85 per cent. (Sahli) white blood cells, 7,000 Differential count polymorphonuclear 50 per cent. lymphocytes, 44 per cent. monocytes, 4 per cent. eosinophiles, 1 per cent. bandforms, 1 per cent. blood sedimentation rate 19 hours 45 minutes (Luzenmmer) blood sugar 105 mg per cent. blood amylase, 50 unites (Somogy). Takata Ara reaction negative. Urine No pathological findings. Stool examination did not show any parasites, culture for bacillary dysentery was negative. X ray picture of the liver region showed no abnormalities.

#### CLINICAL COURSE

Because of the relationship between the ingestion of the powder which we were told contained small amounts of quinine hydrochl. and the appearance of an attack, hypersensitiveness to quinine was suspected. This was more

probable because of the precipitation of an attack by intramuscular injection of quinine. In order to verify this suspicion a patch-test with quinine ointment (quinine hydrochl. 0.1, vaselin albi 10.0) was performed. A small amount of this ointment was put on a piece of lint which was attached to the right fore arm. The lint was covered with gauze and kept in place with a bandage. On the other arm a control test with vaseline only was applied. After 24 hours a positive reaction was seen on the right forearm i.e. a red weal measuring 2 to 1 cm. The control test was absolutely negative. A few days later we tried to provoke an attack, 0.1 gramme of quinine hydrochlor was given *per os* at 2 p.m. At 4 p.m. the patient complained of headache and nausea, which was followed by vomiting. The temperature rose to 38.6° C. He was very restless, his face showed an expression of fear and at about 5 p.m. a severe rigor lasting a quarter of an hour set in and the temperature rose to 40° C. Severe pain in the whole abdomen which was extremely tender on palpation and bloody diarrhoea accompanied the attack. The stool was instantly examined and only erythrocytes and leucocytes were found. There were no amoebae or other parasites. A white cell count which was taken at the height of the attack showed a decrease in the number of leucocytes to 4,000. At the same time the blood pressure dropped from 120/95 to 100/70. After another 2 hours the temperature returned to normal, and all the symptoms disappeared with the exception of headache and fatigue.

#### COMMENT

Though cases of acquired quinine idiosyncrasy, occurring in susceptible persons, who have previously received quinine for varying periods and were thus sensitized to the drug have been described by various authors (HAUER, 1935 NATALLI JACOBSON, 1931 SETTLE, 1938 GRAY, 1922 DAWSON 1930), a primary hypersensitiveness has only as far as we know been reported by HAUER (1935). The absence of previous exposure to and contact with quinine in the past history of the patient, may justify our assumption that in our case we are dealing with a primary idiosyncrasy. The form of reaction which followed the intake of small amounts (0.1 gramme) of quinine is also remarkable. Most cases of quinine hypersensitiveness show skin eruptions (urticaria dermatitis, eczema) as well as vomiting swelling of the tongue and throat, dyspnoea and diarrhoea, but rigor hyperpyrexia, diarrhoea, cramplike pains in the abdomen, vomiting and headache have only been observed in two cases (HAUER, 1935 NATALLI). Similar symptoms following the intake of amidopyrin were recently described by ALVAREZ (1941).

The recognition of quinine idiosyncrasy is especially important in malarial regions where this drug is so often used. The similarity of a quinine reaction to an attack of malaria, as in our case may lead to a false diagnosis. The continuation of treatment with quinine may further aggravate the patient's condition and possibly be followed by shock.

## SUMMARY

A case of quinine idiosyncrasy is reported. The skin reaction to local application of quinine was positive. The main symptoms were rigor hyperpyrexia, diarrhoea, cramplike pains in the abdomen, vomiting and headache. The similarity of the rigor to an attack of malaria is stressed.

## REFERENCES

- ALVAREZ, W. C. (1941) Chills and fever produced by azidopyrim. *Proc. Mayo Clin.*, 16: 760.  
 DAWSON, W. T. GARRARD, F. A. (1930) Idiosyncrasy to quinine. *J. Amer. med. Ass.* 94: 64.  
 GRAY, ST. G. B. D. (1922) Idiosyncrasy to quinine injections. *Brit. med. J.*, 1: 200.  
 HAUSER, A. (1935) Über Chinaminorisation und Chinamidiosynkrasie zu Chinin. *Dtsch. med. Wochschr.* 61: 337.  
 JACOBSON, E. (1931) Ein Beitrag zur Chinamidiosynkrasie. *Ibid.* 57: 1370.  
 NATALLI—cited by HAUSER, A. (1935) Über Chinaminorisation und Chinamidiosynkrasie zu Chinin. *Ibid.* 61: 332.  
 SEXTON, R. O. (1906) Dermatitis medicamentosa. *J. Amer. med. Ass.*, 104: 1801.

# TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

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VOL. XXXVII No 4 FEBRUARY 1944

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## ORDINARY MEETING

of the Society held at

Manson House, 28, Portland Place, London, W ,  
on

Thursday, 18th November, 1943, at 8 p.m

THE PRESIDENT

SIR H. HAROLD SCOTT KCMG M.D. F.R.C.P. F.R.S.E.,  
in the Chair

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## PAPER

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### A SURVEY OF TROPICAL DISEASES AS SEEN IN THE MIDDLE EAST

BY

THE BULMER, O.B.E. M.D. F.R.C.P. LT-COL. R.A.M.C.

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#### INTRODUCTION

From March 1941 to February 1943 I was in charge of the Medical Division of a hospital in Egypt. By the piped distribution of purified water a camp had been laid out in this desert to hold about 100 000 troops served by a group of large hospitals. Troops were always coming and going some newly landed, a few going home, reinforcements being hurried to and from the Western Desert, battle worn troops from operational fronts, resting and re-equipping. There was a steady flow of local sick, and an equal number of admissions from forward medical units by hospital train. The patients were chiefly of British stock, but a native section of 48 beds gave some opportunity of seeing non-indigenous tropical diseases.

We worked at high pressure and my Division treated 17 000 patients in 2 years, yet the sickness rate was low and the average beds occupied by



sick and wounded was but 8 per cent. of the Force a small figure when it is realised that few could be "sick in quarters" and there were no Camp Reception hospitals the proportion of medical to surgical admissions to our hospital was three to two a low figure. As we were not a specialist hospital our patients were unselected admissions and my figures are probably a fair sample of the disease incidence in Egypt and Libya.

Our object was not research the laboratory staff was small, and often overtaxed even by routine work there was usually a shortage of medical officers, and each had 100 to 140 beds our sole duties were the rapid restoration of men to fighting fitness or the relegation of the subnormal to an appropriate category and their unnecessary retention meant a serious depletion of the scanty reserves the climate was not a stimulating one, and we all felt the well-known lethargy of our neighbours the fellahren. Perhaps this will explain the pitifully few garnerings from our wealth of opportunity.

### *Working conditions*

The hospital had 1,200 beds in a crisis expanded to 1,500 three-quarters were in marquees or small tents (E.P.I.P.) for isolation, the rest in Nussen or wattle and daub huts. The site was sandy gravel there were few wet days and the winters were not cold, so that the conditions were well adapted to the climate, and the main discomforts were winds heat and sandstorms. In the second year electricity was installed throughout and replaced hurricane lamps in wards and living quarters hot water was available from cisterns heated by steam centrally generated conservancy was by deep trench latrines and, for infected stools, Orway pits. Diet drugs and equipment were the same as in a military hospital in England or the B.E.F. but at times shipping losses caused difficulties in supplies.

Excellent canteens and a good cinema were provided, and convalescent depots were available and freely used.

### *Training of Medical Officers*

I was impressed by the high standard of knowledge the sound grounding in general principles the keenness and the adaptability to strange conditions and new diseases of the numerous British and Dominion medical officers I had under me.

Nevertheless for military purposes there is room for improvement. Each medical officer has a 2 weeks course of tropical medicine before going abroad, and this cannot be modified for those going to India or West Africa or the Middle East. As a supplement to such academic instruction a few weeks training in the medical wards of a military hospital abroad would be invaluable. The hospital staffs are familiar with local problems, but all too frequently the early treatment of acute tropical diseases was in the hands of medical officers newly arrived in the country unfamiliar with its diseases or their treatment, and in the fighting zones quite inaccessible to skilled help.

This could be corrected by the posting of each new medical officer to a Military hospital in permanent or temporary exchange for a trained medical officer from the hospital. Two weeks posting to the Medical Division of a hospital each year would also help to keep the field force medical officer up to date, and to give him the clinical opportunities which he lacks but is keen to have.

Higher authorities are fully aware of the desirability of such local training but it is seldom practicable under conditions of modern warfare.

### TROPICAL DISEASES

Seventeen thousand odd medical cases passed through the hospital during the 22 months it was working in Egypt, and I have analyzed 13,500 consecutive admissions for the first 18 months, the remaining 3,500 cases in the last 4 months are comparable. 45 per cent. of medical admissions were for tropical diseases and if desert sores be included the figure would be about 50 per cent.

TABLE I

6 141 CASES OF TROPICAL DISEASES

Dysentery Group	4 178	68 per cent.	} 90 per cent.
Short term fevers	1 163	19 "	
Malaria	735	12 "	
Avitaminosis	34	} 1 per cent	
Relapsing fever	19		
Bilharziasis	18		
Kala-azar	6		
Leprosy	1		
Effects of heat	1		

Ignoring the interesting but unimportant 1 per cent., two-thirds of the tropical cases were admitted for acute diarrhoea, and one-third for pyrexia with possibly splenomegaly. These 6,000 soldiers were in hospital for 2 to 3 weeks, with often another week at a convalescent depot.

The incidence of the non-tropical group of diseases was similar to what is found in England with one notable difference the low admission rate for chronic dyspepsia of 4 per cent.

If selected and fit men are sent to the Middle East they suffer from the same diseases and probably to the same extent as in England, but hospital admissions would be doubled because of the occurrence of acute diarrhoea, malaria and sandfly fever.

### ACUTE DIARRHOEA.

Probably every soldier in the M.E.F. had at least one attack of acute diarrhoea usually soon after arrival some considerable degree of immunity

must have been acquired and the rarity of acute diarrhoea in our second summer was the subject of comment although new troops in the area were badly affected. Not all cases of diarrhoea were admitted to hospital, and Major J. H. L. EASTON from a study of the books in the MI rooms in the district thought that only about 6 per cent of those reporting sick were sent to hospital.

The seasonal incidence of diarrhoea is well known although hospital admissions varied according to the fullness of the camp: the winter months produced few cases whilst there were peaks in early and late summer—the drop in numbers in high summer being associated with fewer flies.

An instructive military lesson was supplied when powerful reinforcements arrived in the critical August of 1947: part of a famous division arrived in our area after a quick voyage from the United Kingdom and the subsequent story of the Division leaves no doubt about their fitness, toughness and discipline. Yet had they by force of circumstances been forced to fight within the first few weeks of their arrival I should doubt their ability to have done so and this would apply to any troops landing at that season in Egypt. Our hospital was flooded with cases of acute diarrhoea, in 1 day ninety new cases were admitted and I had 450 beds occupied by dysentery cases for a short time. One battalion alone had 350 men in hospital during a period of 3 weeks and in 1 day 180 of them were warded with diarrhoea. Clearly the ravages were greater than usual and many more than 6 per cent were admitted, perhaps owing to the inexperience of the unit medical officers. Unsalted troops would have difficulty in pursuing an invasion of such a country at such a season, salted troops could however succeed—during the period our own unit was almost free from dysentery.

I cannot add anything but impressions to the reasons for the spread of diarrhoea. In any military community and in any climate, brief attacks of mild diarrhoea keep on recurring—I have seen this in England and in France. Whilst in Egypt throughout all seasons this inconvenient diarrhoea kept on in our wards, perhaps once a week, and quite eluded all attempts at solution: it appears to be a mild food poisoning and not dysenteric. The more serious dysenteric outbreaks are probably spread by the "dust of dried dejecta" and the "repulsive regurgitations, dangerous droppings and filthy feet of faecal feeding flies fouling food".

Its incidence was very low when flies disappeared in the winter and in the extremely hot midsummer weeks whilst it was common experience that the disease was always worse in the field when enemy territory with its neglected sanitation was occupied. The dysentery rate bore a relation to camp hygiene and anti-fly measures, yet the disease has never yet been controlled in war and that our hospital should admit an average of sixty cases a week for 18 months shows how unsatisfactory the position is.

I am unable to my lasting regret to tell you about the problem as seen

by the medical officer in the field of operations as I was not sent forward. I deplored the lack of uniformity in treatment as described in the Field Medical Cards of patients reaching us—salts or castor oil alternating with chalk and opium or opium pills were favourite combinations of pharmacological incompatibles. The forward units lacked specific drugs but many medical officers lacked practical knowledge of how to manage dysentery cases as they had not had the advantage of training in a base hospital. Had the special knowledge and judgment of an officer who had had charge of dysentery wards been available in the field, with a supply of specific drugs, a large number of men would have been retained in the line—indeed many men were quite cured when they reached us—and a standard method of early treatment might have been established.

#### DYSENTERY AS SEEN IN A MILITARY HOSPITAL

Apart from our trivial and recurrent ward outbreaks of mild food poisoning, which I dismiss, minor diarrhoea and true dysentery were to us the same disease. Every gradation of severity was seen in affected units at the same time: why ascribe the mild "guppy tummy" to the ingestion of sand or a draught on the abdomen at night or some other curious theory and incriminate the dysentery bacillus for the severer forms? The selective media now available should establish the clinically irresistible conclusion that they are the same disease: we did not have them, the pathologist would only culture shreds of infective mucus and we were asked not to waste his time by submitting faecal specimens.

General BIGGAM has drawn my attention to the work of PERRY and BENSTED in 1929 in Cairo which certainly suggests that most cases of acute diarrhoea are due to bacilli of the dysentery group.

I shall not describe the clinical features of dysentery to you but our clinical classification of 4000 odd cases may be of some value. Cases were rapidly divided by inspection of stools into those who did not pass blood and mucus and those who did: the former—the *mildest group*—we called "acute catarrhal enteritis" (guppy tummy) as this did not require notification and it accounted for 56 per cent: those who passed blood and mucus were called "clinical dysentery": 20 per cent were *mild*, 22 per cent were *moderate* and 2 per cent were *severe*. The more experienced the person inspecting the stools the more cases he had of clinical dysentery and sigmoidoscopy of the "mildest" group showed some degree of colitis. Severity is an arbitrary thing to assess: I have seen no case of dysentery since my return who would have been sent into a hospital in Egypt whilst our mildest cases were too ill to be treated in their units. Life was threatened in all the "severe" cases. The average duration of stay in the "mildest" group was 10 days of the clinical dysenterics 20 days in two series of 600 cases including sulphaguanidine treated cases.

*Treatment* To control progress a graphic method of charting the frequency of stools was used with a daily description of a morning specimen. Our treatment was very simple—strict rest in bed and, to conserve strength in severe cases, the use of a modified baby's napkin—a dysentery pad—water only by mouth for 12 hours, then a graduated bland diet until the stools were normal. Morphine was given to relieve severe pain—no other medicinal treatment was used except sulphaguanidine in selected cases, and we had no regrets about our early disuse of salts or castor oil. Dehydration was very rare, transfusions of plasma or whole blood were used to correct it.

Dysentery was for us a clinical problem and its treatment was guided by our general impression of the patient and his stools, the presence of a tender iliac colon being a valuable indication of severity and sigmoidoscopy essential if there were frequent or abnormal stools after a week. I think the attempt to isolate the dysentery bacillus has become a fetish, quite impracticable under field conditions and giving no timely help in treatment—it is as reasonable to withhold antitoxin until the positive diphtheria swab returns, as it is to withhold sulphaguanidine and Shiga serum until the stool culture is reported on—for success prompt treatment on a clinical assessment is essential.

In our large number of isolations the percentages were Flexner 70 per cent., Shiga 19 per cent., Sonne 6 per cent., Schmitz 5 per cent.

In cases of over a week's duration laboratory help is essential to exclude amoebiasis—it is preferable to have the pathologist present at the sigmoidoscopy with his microscope.

Probably the ideal would be for the medical officer in charge of dysentery wards to carry out his own microscopic examinations in an improvised clinical room and this would be essential in a district where there was much amoebic dysentery. I understand this was done successfully in North Africa, but it would entail the capture of a fair number of additional microscopes.

#### SULPHONAMIDE TREATMENT

As Lt-Col PRIEST and I\* have already published our impression of nearly 500 cases I shall merely give a summary here.

1 *Sulphamylamide* Sixty-three cases were treated and the experiment discontinued on account of poor results.

2 *Sulphapyridine* Ninety-seven cases were treated—the results were nearly as good as with sulphaguanidine but nausea vomiting and malaise were so marked that we felt its use was only justified when sulphaguanidine was unobtainable.

3 *Sulphathiazole* *Sulphadiazine* *Succinyl-sulphathiazole* Supplies were inadequate for a trial. I feel that the cheap sulphathiazole with its low

BULMER, E. & PRIEST, W. M. (1945) Bacillary dysentery. Chemotherapy in its treatment. *Lancet* 2, 69.

toxicity would be ideal for field use if its action approaches that of sulphapyridine.

#### 4 Sulphaguanidine

"Gypsy tummy" I know that many Sisters and M.O.s treated themselves, and did not go sick. Seventeen patients were treated with an average stay in hospital of 6 days. Many of us remained on duty whilst on ambulant treatment for actual dysentery—it was perhaps a point of honour but the experiment justified itself it is however inapplicable to the cases with a brisk febrile onset. This was done by the Australian troops in the South West Pacific with excellent results.

*Dysentery proper* Three hundred and six cases were treated. The important points can be briefly summarized —

##### 1 Indication

(a) *Ideally* every diarrhoeal case of sufficient severity to be admitted to hospital it is as irrational to discriminate between grades of severity as it would be in pneumonia, meningitis or gonorrhoea if saving of man-power as well as life is an object.

(b) *With limited supplies* (1) All severe cases (2) Moderate cases not doing well or persisting after a week (3) Mild cases—key personnel only

ii *Dosage* Large doses must be given, and continued until the stools have been normal for a day or two 350 grammes was our maximum, 100 grammes the average, and 30 to 40 grammes adequate in early cases. A safe system was 6 grammes at first 3 grammes 4-hourly until the stools are two to three daily then 3 grammes thrice daily for 2 to 3 days, but this dosage was doubled in very serious cases.

iii. *Toxicity* Subjectively there were no toxic effects. We had four cases of rubelliform rash about the 10th day and one case of sulphaguanidine kidney which recovered.

iv *Results* There is a rapid general action—the feeling of misery or malaise quickly goes and an apparent de-toxication occurs we all observed this, and both Priest and I have experienced it. The dysenteric symptoms rapidly abate—pain goes the stools diminish in number and improve in appearance—the resolution of the inflammation was sigmoidoscopically followed in many cases.

Figures are perhaps much less impressive to us than our clinical impressions—but they support the value of sulphaguanidine.

(a) Of 203 acute cases treated, and these included every severe and nearly every moderate case with some mild ones, the average stay in hospital was 17 days stools at the beginning of treatment sixteen on 5th day two to three on 7th day normal. In 600 consecutive cases of all grades of severity and all methods of treatment the stay was 20 days.

(b) *Control series* Thirty-six moderate cases were treated with the drug

on admission and thirty-six moderate cases without it—they were as comparable as possible, the control series being less severe.

(c) *Subacute and chronic cases.* If a specific bacillus could be isolated the response was good: one case of 6 months standing whose apparently amoebic ulcers gave a culture of bacillus cleared up in a week.

(d) *Death.* In the present series there were two deaths, but we had two later deaths so the final mortality rate for dysentery excluding those not passing blood or mucus was about 0.16 per cent or under two per 1 000.

TABLE II

	Stools per day on admission	Stools on 7th day	Stools normal (days)	Stay in hospital (days)
Controls	40	4	9	16
Sulphaguanidine cases	21		6	11

One died on the 15th day but he only had 1 day's treatment: two cases reached us with pericolic abscesses: one case of Shiga dysentery was treated from the 3rd day and died in spite of sulphaguanidine serum, transfusion, etc.

(e) *Sequelae.* Only a long follow-up will show ultimate results. I know of only one who will probably have chronic ulceration, and during most of the time we could hold our cases until they were fit for duty—a few were transferred to Palestine semi-convalescent during the Alamein battle and lost sight of.

#### Serum Treatment

In only eight cases of Shiga dysentery was serum used since sulphaguanidine results suggested that it was unnecessary.

#### Flagellate Dysentery

In a few chronic cases of diarrhoea *Giardia lamblia* was found in the stools and a course of stebrin rendered the patients symptom-free.

#### Choleraform Diarrhoea

No true cholera was seen but an alarming minor outbreak of diarrhoea reproduced faithfully the picture of cholera, with the typical stools: the patients did not seem ill enough for cholera, and all recovered rapidly.

#### Amoebic Dysentery

I am dissatisfied with the record of a low incidence of amoebiasis—1 per cent—we did not miss any cases of hepatic amoebiasis as the morbid anatomist

had an opportunity of confirming the diagnosis in all deaths—an empirical use of emetine in suspicious cases and an awareness of the possible meaning of unusual right basal infections saved our patients of whom we had about ten. Every effort was made to diagnose amoebic dysentery: the proved cases did not show the typical old chronic ulcers I have seen in England but I came to regard a curious gelatinous oedema of the mucosa as characteristic of the acute type amoebic dysentery of the proximal colon only may escape detection as the pathologist has to depend upon bed pan specimens and has not the same chance of finding the motile amoebae as when he is working in the same room with the sigmoidoscopist.

Our standard treatment of amoebic dysentery was 10 to 12 grains of emetine then 4 grains of stovarsol twice daily for 10 days, and finally 3 grains orally of emetine-bismuth iodide daily for 10 days. I did not have a relapse admitted after such courses elsewhere whilst the use of quinoxyl instead of E.B.L. gave us several from other hospitals—I have recently had a confirmation of such relapses from a colleague in Tripoli. Doubtless others saw our relapses, and it is impossible to draw conclusions from these impressions.

#### SHORT TERM FEVERS AND MALARIA.

Half of our medical admissions were for commonplace "English" diseases one-third for diarrhoea, and one-sixth for short term fevers. Two thousand patients were admitted with a similar clinical picture—pyrexia often heralded by a rigor severe headache, vomiting and often pain on moving the eyes: there were no signs beyond frequent splenomegaly and pink-eye. We had few cases of M.T. malaria and no pernicious forms, so that we could usually temporize and we withheld quinine unless the patient was very ill or had hyperpyrexia.

The lapse of time gave us the diagnosis in some cases, dysentery jaundice one case of poliomyelitis: the laboratory helped us in others—735 cases had malaria and nineteen relapsing fever: in 1153 cases the patient recovered in a few days: we thought 805 of them had sandfly fever but were not too sure of this and were quite at a loss over the remaining 348.

The first sandfly was discovered by Professor P. A. Buxton on 6th April 1942 so we could with some support call our short term fevers sandfly fever: quite similar cases occurred in the winter and patients with classical symptoms of sandfly fever were proved to have malaria. I hesitate to diagnose sandfly fever with any certainty in the absence of an epidemic—one patient after a typical attack developed extensive paralysis from poliomyelitis: another had his third attack of sandfly fever in another hospital and was shown to have relapsing fever.

I suggest the name "short term fever" for this group: it reveals one's ignorance of the cause of nearly 10 per cent. of the medical admissions and further research may find several new diseases. Its management is quite



sample twice daily blood films for 3 days, the retention of suspicious cases for 2 weeks so that there is time for a further attack of relapsing fever to occur and the administration of quinine should splenomegaly—clinical malaria—develop. With the large numbers involved neither early blood culture nor a routine leucocyte count was possible, and full investigation had to be reserved for cases going on longer than 5 days.

### Malaria

We had 735 cases (BT 81 per cent., MT 6 per cent., Quartan 1 per cent. clinical 11 per cent.), but I saw only one dangerously ill man—he had flown through Central Africa—experience impressed us with the protean manifestations of the disease, but not with its deadliness—a dangerous impression if we had suddenly been sent to other areas. Our worst cases came from Crete during the brief early summer campaign there in 1941.

The treatment was standardized: quinine until afebrile, then atebryn 0.1 gramme t.d.s. for 5 days and then plasmoquine 0.01 gramme t.d.s. for 3 to 5 days: the relapse rate was low but we had a good many relapses in South Africans who had not had plasmoquine.

The only death was from acute haemolytic anaemia during the plasmoquine course, perhaps a coincidence as we had two similar cases, one following sulphapyridine and one idiopathic.

### THE 1 PER CENT OF TROPICAL DISEASES

Medically fascinating but of no military importance owing to the small numbers involved yet brief mention of some of them must be made. The group is made up of pellagra thirty-one beriberi three, relapsing fever nineteen, bilharziasis eighteen kala-azar six, leprosy one effects of heat one.

#### Pellagra. Thirty-one cases

In the summer of 1941 an interesting outbreak occurred. At a nearby P.O.W. camp housing about 10,000 Libyans the occurrence of scurvy had led to a modification of diet by increasing vegetables at the expense of the meat: the diet was roughly bread 24 oz. meat (raw) 1 oz. cotton seed oil 2½ oz. salt species vegetables but no milk, eggs or offal. Many cases of diarrhoea occurred in the spring and in a fatal case Major R. POLVERTART raised the question of pellagra. Examination revealed over 1,000 cases of typical pellagra of whom about 200 were moderately severe and thirty-one very severe. These latter I had in hospital, put them on a full diet with 100 mg. of nicotinic acid, and saved all but one, who died from T.B. In the camp the diet was at once suitably modified by adding milk raising the meat ration to 6 oz. and issuing peanuts. The clinical features were the usual ones, but neurological and mental changes were almost absent.

#### Beriberi. Three cases

A few cases occurred in the long distance desert groups, and in the

besieged Tobruk garrison. We had one fatal fulminating case of mixed beriberi, and two milder cases who recovered on a mixed diet and 150 mg of vitamin B<sub>1</sub>.

#### *Relapsing fever* Nineteen cases

Tick-borne relapsing fever occurs in Palestine, Crete and the caves round Tobruk as well as other parts of the Levant. It proved at first a puzzling disease—the tick bites unobtrusively and most patients were unaware that they had been bitten spirochaetes are very scanty in the blood the neurological complications of lymphocytic meningitis, or cranial and other nerve palsies or both combined, were for us unexpected the disease was resistant to most drugs but I thought stovarsol was effective the febrile attack was brief and similar to early malaria and sandfly fever

Latterly we felt we could make a clinical diagnosis after a few relapses but I believe a correct diagnosis was seldom made in the first bout.

#### *Bilharziasis* Eighteen cases

Fifteen cases were in Mauritians who came to Egypt with it one case was in a Senussi two only were in white troops one infected in Durban and one at Ismailia, probably whilst watering a garden with water from the Sweet Water Canal.

It was a dull disease—terminal haematuria or cystitis as the symptoms—and the only thrill was seeing a miracidium hatch out Its interest is its practical absence, a tribute to the troops' good water discipline.

#### *Kala-azar* Six cases.

This was of the peculiar Sudan type, with difficulty in finding leishmania, and resistance to antimony with a dramatic response to neo-stilbene. One of our cases was from an endemic zone in the Cameroons the others were contracted in a localized area of the Sudan where large numbers occurred. The first case quite baffled us—a typhoid-like illness with marked leucopaenia and splenomegaly as soon as we were aware of the existence of the disease in the Entrecan front we watched for cases, and discovered the other three. The Laboratory helped but little as the formol-gel test was only twice positive, and we found leishmania only once The cases all went to Cairo and all cleared up with neo-stilbene

#### *Effects of heat* One case.

Although every preparation was made for cases of heat hyperpyrexia both by direct admission or as a complication of diseases under treatment, we had none hyperpyrexial cases occurred but were all due to infections We were in a region of low humidity although shade temperatures commonly exceeded 105° and once reached 120° F

It is probable that this war will lessen the popularity of the topee—in the Middle East merely a clumsy headgear that finally became optional The

experimental work done by MARSH in Persia on rabbits, and presented to this Society should have rung its death knell a decade ago.

One fatal case of heat exhaustion occurred—a soldier who had had an attack in the Red Sea arrived in Egypt during a heat wave. He was admitted with a week's history of anorexia, weakness and loss of weight, had a blood pressure of 62 mm. of mercury with a blood count of 6½ million red cells, and 130 per cent haemoglobin. He developed anuria, and died of some type of renal failure, the blood urea being 370 mg per cent. He failed to respond to fluids by all routes. The autopsy gave no further clues.

### CONCLUSION.

Let me crave your indulgence for a very free expression of opinion, by a tropical veto, on your special subject. I should speak of these matters with less assurance had I twenty instead of two years' experience.

### DISCUSSION

The Chairman (Sir Harold Scott). Gentlemen, as regards Colonel BULMER's paper I have nothing to say at present—in fact, the less I say the better—so many people would like to speak who are more *au fait* with the subject. The ratio of three medical cases to two surgical in war time is unusual if not unique. When one thinks of previous wars before the last the proportion was twenty or more medical to one surgical. Again, the characters of diseases seem to alter from time to time. In the South African war I had a large number of cases of dysentery under my care, and I found that the concentrated sulphate gave wonderful results instead of negligible, as Colonel BULMER found in the present campaign. Patients used to react in 24 to 48 hours and stools would be reduced in number to three or four in that time. Such treatment was found to succeed in the bacillary form only, not in the amoebic. We used to give it in doses of 10 grains in a drachm every hour till the stools became faeculent.

Lt.-Col C H Barber. I would like to ask Colonel BULMER the result of treatment by dysentery serum? He only used it in eight cases, with good results in one. Was the good result due to sulphaguandine? In the other seven cases it would be interesting to know the effect of the serum. I was glad to hear Colonel BULMER's comments on the topee and heat stroke. I think the effects of heat are most often due to the body getting overheated not from the rays of the sun but largely from radiation from the ground. You do not get it in the hill stations where the sun is still stronger. I have long advocated a topee or hat made of light straw which does not heat the head and yet protects from the sun's rays. There were experiments years ago on the effect of the direct rays on monkeys' heads—before the experiments on rabbits—and it was shown that you could expose a monkey's head for hours to sun without harm provided you kept the body cool. Talking about pellagra, it was not clear whether

protein was added as well as nicotinic acid, or whether the amount of protein was reduced

Sir Phillip Manson-Bahr congratulated Colonel BULMER on his excellent and essentially clinical paper. As one who during the last war had on many occasions been overwhelmed by avalanches of bedpans, he could sympathize with the question of prompt diagnosis of bacillary dysentery. When he compared the record of sixty cases of dysentery a week with as many as ten times that number during the Gallipoli epidemic in 1915 and in Sinai in 1917 it showed what a remarkable change had occurred in the incidence of bacillary dysentery. It was at that time quite impossible with the limited laboratory facilities at our disposal to attempt anything in the way of large scale isolation of specific dysentery bacilli, and therefore it is possible to agree that the introduction of sulphaguanidine treatment has rendered these bacteriological refinements from the practical viewpoint, unnecessary. The mere statement that under this treatment the average case was passing normal stools within five days was ample demonstration if further proof were needed of the efficacy of sulphaguanidine treatment.

Recently there had been some closely argued criticism that the claims of bacteriophage treatment elaborated in Alexandria had been neglected. Extravagant claims had been put forward and he had met many who stated that its effects in "gypsy tummy" and other explosive diarrhoeas had been widely recognized and that this treatment had much support in the Navy. He, himself had remained unconvinced, as he was unaware of any carefully controlled series of cases subjected to bacteriophage treatment, and he would be glad if this bogey could be laid to rest.

As regards the outbreak of pellagra in Italian prisoners, he could not fail to be struck by the way in which that history under similar circumstances in 1916 had repeated itself. But what a change had been effected in treatment of this disease by nicotinic acid! Most assuredly in those far-off days the great majority of these acute cases would have succumbed.

As regards the great group of pyrexias of uncertain origin he would like to enquire whether sternal puncture, on which several papers had recently appeared was found to be of real value in diagnosing obscure or evanescent infections with *Plasmodium falciparum*. It would appear that this might be a valuable method, for 25 years ago there was, as now a tendency to lump all febriculæ together under the convenient camouflage of sandfly fever. Subsequently many of these cases relapsed and were found to be in reality subtertian malaria.

Professor P. A. Buxton. In the beginning of his paper Colonel BULMER gave an account of that enormous camp in the desert roughly between Suez and Cairo. There was one point about it, which interested me very much when I lived in it in 1942, a point to which he did not refer. In that large group of

this must be taken as local, as it is not the proportion of medical cases to battle casualties throughout Middle East.

As regards the early bacteriological diagnosis of dysentery I agree that the necessity for this has been changed by the introduction of the "sulpha" drugs. We have now given up the routine bacteriological examination of dysentery stools, but I do not regret that we adopted it for the first few years. It has given us a clear idea of the incidence of the different types of dysentery and has proved excellent training for pathologists who had no previous experience in that type of investigation. I might have brought with me an analysis of some 60 000 cases of dysentery. It will interest you to know that the percentage of amoebic dysentery was less than 5 and that, of the different types of dysentery bacilli isolated, *Shiga's bacillus* comprised approximately 20 per cent.

As to serum treatment, I think Colonel BULMER's ideas would have been different if he had been in Middle East in the pre-sulphaguanidine days. At that time I saw with Colonel HAMILTON FAIRLEY a number of very severe cases of bacillary dysentery. Such cases have been rare in later years and I attribute this largely if not wholly to early treatment with sulphaguanidine. For *Shiga* infections we used a concentrated antitoxin in doses of 100 000 units. This produced an immediate amelioration of symptoms lasting about 24 hours, but thereafter the patient's condition again deteriorated. We formed the opinion that if serum was given at an early stage it had a more permanent effect because it allowed the patient's natural processes of defence to come into action, but in later stages the effect was temporary only. We came to the conclusion that the best treatment for acute toxic cases was a combination of sulphaguanidine and antitoxin. Nevertheless what Colonel BULMER says is correct, and nowadays in sulphaguanidine-treated cases there is very little need to use serum.

We have been increasing greatly the use of sigmoidoscopy and have found some unusual pictures. I think some existing conceptions may need revision in the light of this experience. Colonel BULMER referred to one such case.

SIR PHILIP MANSON BURN has raised the question of bacteriophage therapy. If I may I shall say a few words about this, as we have carried out some investigations subsequent to Colonel BULMER's departure. In the advance to Tunisia we captured large quantities of German medical stores including an excellent polyvalent bacteriophage which was the standard treatment for bacillary dysentery in the German army. We divided a prisoner-of-war camp into two sections, and treated all cases of bacillary dysentery in one section with standard bacteriophage treatment, and those in the other half with ordinary saline treatment. Bacteriophage treatment was started the moment a patient complained of any intestinal symptom. Admission rates for dysentery were practically identical in both sections, and the duration and severity of the disease were not dramatically different. If anything the figures in the bacteriophage

series were slightly better but the difference was not statistically significant. We also carried out an experiment in prophylaxis along the lines recommended by a German observer. All the inmates of one cage were given bacteriophage on three successive days. Contrary to what has been claimed elsewhere, the subsequent incidence of bacillary dysentery in those so treated did not differ from that in untreated cages. There was no evidence of prophylactic action.

In addition we had an unexpected confirmation of our findings. In a certain area there is an internee camp in which considerable numbers of enemy aliens (chiefly Italians) are confined. These enjoy certain amenities, including the privilege of being visited by relatives, who come periodically bringing presents, including large quantities of bacteriophage, which is taken prophylactically and as treatment. Nearby is an Italian prisoner-of-war camp in which no bacteriophage is used. The sanitation of the two camps is identical in both cases under our military control. We were able to get figures of the admissions for dysentery in the two camps over a period of months, and found that the prisoner-of-war camp was rather better than the other.

Colonel BULMER said he had a case of malaria with haemolysis due to plasmoquine. I would like to know how he decided it was plasmoquine poisoning and not blackwater fever.

Colonel BULMER mentioned some 100 cases to which he was compelled for want of a better to apply the diagnosis of sandfly fever. I think this diagnosis is run to death. It is probable that the majority of these cases were not sandfly-fever and I think it would be much better if we used an honest diagnosis such as pyrexia of unknown origin stating the number of days of fever e.g. P.U.O. 3 day P.U.O. 5 day etc. This might lead to the differentiation of types which are at present camouflaged under the blanket diagnosis of sandfly fever.

As regards pellagra and diet, apart from the actual scale of rations provided there is another factor to be considered. Some of these native races refuse to eat certain components of the diet provided for them. A diet may be in every way adequate, yet for the above reason fail to prevent deficiency disease.

The President. I would like to interpolate a word with regard to what one contributor said about desert sore. I can trace it a good deal further back than he has done. When I was in the R.A.M.C. in the South African war I saw a good deal of veldt sore. We got no results from ordinary treatment of ulcers until I examined them and found the diphtheria bacillus in the discharge. I was then able to get antitoxin and applied swabs soaked in antitoxin to the sores and they cleared up wonderfully. One case had definite post diphtheritic paralysis. That was in 1901.

Lt-Col Bulmer (in reply) hoped that he had not given rise to misconceptions by compressing the subject unduly. He thanked Colonel Boyd for dealing with bacteriophage in the treatment of bacillary dysentery.

Many speakers had spoken of the value of Shiga anti-serum—he thought the introduction of sulphaguanidine had made its use seldom necessary but he had no experience of the results of serum treatment alone. The orders from the Medical Directorate in the Middle East were that serum must be used on all serious cases of Shiga dysentery—the speaker had accepted the responsibility of withholding serum in such cases, and using only sulphaguanidine, the response had been as satisfactory as when both were used. The chart shown on the screen which provoked the discussion was intended to demonstrate a simple method of recording progress and not the value of specific treatment which could not be judged from a few striking charts.

The treatment of the pellagra cases was by giving them a full, balanced diet—to the seriously ill ones nicotinic acid was administered, but riboflavine was not available.

Sir PHILIP MAXTON BAKER's questions about bacteriophage had been answered by Colonel BORD. Colonel BULMER did not think that missed cases of malaria accounted for many of the unsatisfactory group of short term fevers, although sternal puncture was not carried out—it was certain that cases of relapsing fever were missed.

The speaker did not agree with Professor P. A. BURTON's suggestion that "gypsy tummy" was not dysenteric, and unsuccessful attempts to isolate the dysentery bacilli were due probably to the absence of selective media.

Air Commodore MORROW's question about the diphtheritic desert sore was of great importance—in the speaker's cases a few showed diphtheria bacilli, one unexpected fatality occurred. In Palestine the Australians, the speaker believed, studied this subject very fully and they did not get positive swabs from the sores until an outbreak of faucial diphtheria occurred in that country. It is probably true to say that desert sores are due to unknown factors, and are not diphtheritic—like any other abrasion or wound, they can be infected secondarily by the Klebs-Löffler bacillus, and a type of wound diphtheria be produced, but in Egypt the number of such cases was negligible.

The patient with heat exhaustion did not have cramps, and he was given salt in large doses, both by mouth and intravenously.

Dr STANLEY's question about where flies, if they are dysentery carriers, can infect food, is difficult to answer—the speaker thought bread was possibly contaminated, as there are ample opportunities between the field bakeries and the unit kitchens.

In reply to Dr FELT, the speaker said that specific anti-sera were not used in the treatment of typhoid fever.

Colonel BORD had raised many interesting points, and corrected several of the speaker's impressions. Colonel BORD had access to the official Middle East statistics, Colonel BULMER had merely his own hospital's records. The fatal case of haemolysis attributed to plasmoquine might have been blackwater fever but could not be dogmatically ascribed to malaria, as parasites could never be discovered.

## COMMUNICATIONS

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### BACTERIOPHAGE THERAPY IN BACILLARY DYSENTERY

BY

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The discovery of bacteriophage by TWORT in 1915 and D'HERELLE in 1917 opened up the possibility of using this agent therapeutically in the treatment of certain bacterial diseases of which bacillary dysentery on account of the superficial and accessible situation of the lesions in the bowel appeared to be *par excellence* one in which it was likely to be successful. Many observers, including D'HERELLE himself claim to have obtained striking results from its use in this disease, but others have found it to be without effect. All trials hitherto made in military practice fall into the latter category and for this and other reasons it has never been adopted as a standard form of treatment in the Army.

Recently a unique opportunity arose to make a thorough investigation of this subject, the results of which are presented in this paper.

#### LITERATURE ON BACTERIOPHAGE THERAPY IN BACILLARY DYSENTERY

Difficulty has been experienced in gaining access to all references on this subject owing to active service conditions. It is believed that the majority of important papers in English have been consulted but many in other languages have not been obtainable. In certain cases it has been necessary to rely on excerpts from *Bulletins* and where the original has not been consulted a note to this effect is made.

DAVISON (1922) (original not available) had a 53 per cent. mortality in twelve bacteriophage treated cases of bacillary dysentery in children. Flexner's bacillus was isolated in ten of the cases and of eight strains tested seven were susceptible to bacteriophage. Large and frequent doses were used—from 5 c.c. to 13.00 c.c. being given. Seven cases were treated orally five by enema. Failure was attributed to the fact that therapy was commenced too late in the course of the disease.

COSTA CRUZ (1924) in a paper which gives no statistics and no figures as to number of cases concluded that Bacteriophage is easily the best treatment for bacillary dysentery. Its action surpasses all other agents—the symptoms diminish considerably in 4 to 8 hours and the illness enters into its convalescent stage in 24 to 48 hours after administration.



SPENCE and MCKENLEY (1924) (original not available) treated twenty cases of Shiga and Flexner infection, nineteen within the first week of the illness with 10 c.c. of bacteriophage t.d.s. orally. The mortality rate was 10 per cent. and the average stay in hospital 5.8 days (a somewhat striking contrast). A control group in another hospital (? number) not treated by bacteriophage had mortality rate of 40 per cent. and an average stay in hospital of 12.8 days.

CHODHURY and MORISON (1929) (original not available) treated eighty cases of Shiga and Flexner dysentery with a polyvalent bacteriophage giving 2 c.c. t.d.s. the 1st day and b.d.s. thereafter. The mortality rate was 4 per cent. No reference to controls is available.

TAYLOR, GRIVAL and THANT (1930) (original not seen) treated cases in which only a short interval had elapsed between onset of the disease and treatment, 2 c.c. of polyvalent bacteriophage was given three times daily. In fourteen cases of Shiga infection there was a mortality of 14 per cent. as compared to 1 per cent. in a control group. In six treated Flexner cases and a control group there was one death in each series.

COMPTON (1929) published a "record of sixty-six cases with inferences". He classified his results as very good thirty-five, good ten, moderately good six, partial failure five, failure ten. But of the failures four were advanced cases before treatment was started and did not have fair chance. No controls were maintained. The bacteriophages used in this experiment were good ones and had been tested *in vitro*. During the treatment a noteworthy lowering in the death-rates from dysentery was observed. Distribution of bacteriophage to patients in a region means an increased proportion of bacteriophage carriers among the population with, in all probability, a correspondingly increased distribution of bacteriophage in the food and drink.

RIDING (1930) observed, over a 2 year period, sixty cases of bacillary dysentery of which records were maintained in forty-eight. Thirty-five were treated with bacteriophage, thirteen were kept as controls. Each case was thoroughly investigated, clinically and bacteriologically. RIDING concludes (a) it is probable that bacteriophage ingested by mouth is quickly eliminated or destroyed by the human body, (b) the contents of the intestines in dysentery do not appear to be suitable medium for the process of bacteriophage, and (c) the clinical course of acute bacillary dysentery is not altered by the oral administration of bacteriophage. RIDING's clinical findings are open to the criticism that most of the patients had been ill for some days before treatment was started.

QUERANQAL and EMMARTS (1933) treated 190 cases of bacillary dysentery occurring in 29 days on board two ships at Brest. Fifty-nine were identified, sixteen Shiga, thirty-eight Flexner and five paratyphoid. 183 were treated with polyvalent Shiga-Flexner bacteriophage prepared from comalescent stools, which was active and proved innocuous. 5 c.c. was given in alkaline water the 1st day, 10 c.c. the 2nd and 3rd days and 5 c.c. the 4th day. The "results were remarkable". After the 2nd or 3rd day blood and mucus disappeared, and after 4 days the stool appeared normal microscopically. None of the cases had severe toxæmia. There were no controls. The author also claims to have averted an outbreak among infants in a holiday camp by giving bacteriophage prophylactically. Again there were no controls.

KHILZI and ROSE (1935) (original not seen) reported sixty-eight cases of which half were maintained as controls. 90 per cent. of the Flexner strains were found to be susceptible to bacteriophage. The dose given was 3 c.c. to 5 c.c. orally every 12 hours. There were three deaths in the control group and four in the treated group. The period of hospitalization was slightly but not significantly lower in the treated group.

JOHNSON, EASE and KAKER (1933) (original not seen) found that bacteriophage did not affect the clinical course of dysentery, seventy infants under 2 years of age were treated with 1 ounce of bacteriophage hourly. Only seventeen out of ninety-four strains tested *in vitro* were susceptible to the bacteriophage employed.

MCCAY (1934) describes the treatment of bacillary dysentery in Calcutta with bacteriophage prepared in Shikong. Anti-dysenteric serum was used in a large proportion of cases. No statistics are given. The author states "I hope that bacteriophage enthusiasts will duly publish a series of such cases with controls. If bacteriophage has no other

claim to success at any rate it cannot be said that it makes the patient's diarrhoea worse than it was or in any way stimulates the intestinal tract.

VAILL and MORTON (1937) treated 200 cases of dysentery with bacteriophage in New Jersey but kept records of only twenty two cases. Figures are given for these which convey little information as only one case is cited as a control. The authors prefer a strain specific bacteriophage which has been adapted to the patient's strain of bacillus by serial passage. At the same time they emphasize the importance of instituting bacteriophage therapy as soon as possible after the onset of the disease. They do not explain how these two paradoxical requirements are to be reconciled.

MURRAY (1938) treated 146 cases of bacillary dysentery with bacteriophage between 1931 and 1937. Usually the treatment took 2 weeks seldom longer than 3 weeks. There were no controls no mention is made of the isolation of organisms nor are details of the bacteriophage given. The author concludes (1) that bacteriophage is by far the best method of treating bacillary dysentery (2) that failure in treatment can be attributed to the fact that a reliable bacteriophage has not been used and (3) that to prove its value a controlled series is required.

HALER (1938) treated an epidemic of dysentery in a home for children—thirty-two children staff of seventeen. There were seven cases of Sonne infection, but the writer also refers to an atypical organism which he believes to have been evolved from the Sonne bacillus by the action of the bacteriophage. This mutation was not substantiated experimentally. Everyone was given bacteriophage (dose not stated) thrice daily for a fortnight and one dose daily afterwards. The epidemic ceased 2 days after giving bacteriophage and there have been no cases for a year. There were no controls and the author states that this cessation of the epidemic may have been a coincidence.

GUTHOF O (1941) (original not seen) a battalion M.O. in a German infantry regiment treated bacillary dysentery with Dysentery Polyfagen (Behring). Fifty two adults were treated with good results in 2 to 4 days and in three children with severe infections the results are also stated to have been satisfactory. No controls are mentioned in the review consulted.

WHEELER and BURGDORF (1941) investigated, as a possible means of establishing a diagnosis the presence of bacteriophage in the stools of patients who had suffered from bacillary dysentery. They were successful in isolating bacteriophage from 3 to 9 weeks after the date of the attack in a number of cases. Several individuals (fifteen according to their tables) gave concurrently positive culture and bacteriophage tests for varying periods of time up to 2 weeks. Organisms isolated from these individuals were susceptible to the bacteriophage strain but apparently the *in vitro* action was not sufficiently strong to eliminate the organisms.

KLIEWE, H and HELMREICH W (1941) (original not seen) stress the importance of ensuring that the bacteriophage used is potent against the local strains. In Poland many of the local strains of dysentery bacilli were not susceptible to German bacteriophages. A test of the prophylactic value of locally prepared bacteriophage mixtures was made by giving 113 soldiers while in a fasting state a dose of sodium bicarbonate followed by 10 c.c. of the mixture in half a cup of tea or coffee on three successive mornings. 250 men of the same unit were left untreated to serve as controls. In the course of the following 8 weeks no cases of dysentery developed among the 113 bacteriophage treated men, while ten cases occurred among the controls. The therapeutic value was also tested. It was said to prove particularly effective in cases of mild or moderately severe Flexner Y dysentery. In cases of severe illness there was frequently an exacerbation and only occasional improvement. sixteen carriers were cured after they had received bacteriophage therapy on 3 successive days.

SOESMAN (1941) (original not seen) reports on fifty cases of bacillary dysentery—seventeen adults and thirty-three children treated with polyphage. All recovered and in most cases the severe symptoms disappeared after oral administration of the bacteriophage.

In our opinion the polyphage is a valuable asset in our armament against the acute bacillary dysentery intestinal infections." No reference is made to controls.

COMPTON (1942) cites case mortality rates in Alexandria, Cairo and the rest of Egypt, and suggests that the falling mortality rate of dysentery in Alexandria is to be attributed

to the use of bacteriophage. The argument is wholly inferential, and is based on figures which do not substantiate claims made elsewhere by this author to wit, that the early use of bacteriophage prevents the development of dysentery. If the latter argument is correct, and if as the author says "it has become the established rule to treat acute bacillary dysentery and its frequent precursor acute enteritis with bacteriophage why is it that "the total annual number of cases of dysentery has averaged about 650 during the period (1922-40) and has not gone down to any great extent

HIGLIA (1943) describes the treatment of dysentery with bacteriophage without giving much detail, and finishes "It is not possible to give a conclusive decision on the value of bacteriophage" (Among the German medical officers HIGLIA is regarded as the leading authority on dysentery and its problems)

Perusal of these references reveals much diversity in result and opinion. It is noteworthy that in the majority of trials no controls have been maintained and that practically all observers who have instituted this check report guardedly or unfavourably on the results obtained.

### PREVIOUS ARMY TRIALS OF BACTERIOPHAGE THERAPY

Prior to the present experiment, four small-scale trials of bacteriophage therapy were made in the Army in Middle East, none of which have been published. Two of these were made before the establishment of Middle East Command, and neither gave results of any promise. The third was carried out by Surgeon-Commander D. C. WILSON, R.N., and Major J. E. JAMESON, R.A.M.C. Here again the results were unconvincing. Correspondence on this trial has appeared in the columns of the *British Medical Journal* (1942, 16th July p. 81 and 5th December p. 676). The fourth was a carefully-controlled trial made by Capt R. P. HENDRY, R.A.M.C. Thirty-two cases were treated, of which eighteen were in the control series, and fourteen were treated by bacteriophage. Capt HENDRY in his report drew the following conclusions.

The general impression gathered from observing the progress of the thirty-two patients in the ward and subsequently from studying the above tables, was that the bacteriophage group made slightly better progress than the control group. But the difference was so small that had an additional dozen cases been treated the result might easily have been reversed.

Against these and other negative findings, the supporters of bacteriophage treatment advance two arguments, one that the bacteriophage used has not been potent against local strains of dysentery bacilli, the other that the treatment has been started too late in the disease. If substantiated, both these objections are valid. As to the first, the bacteriophage used in these Army experiments was a preparation in wide use in Alexandria and Cairo in civil practice, regarding which enthusiastic claims are made by local practitioners. As to the second, while certain of the cases were some days old before bacteriophage therapy was started others were in the early stages, in which good results are said to follow almost invariably. The latter did not respond to treatment any more quickly than the former.

## AN UNPROMPTED EXPERIMENT

Unknown to the writers of this paper an entirely unprompted and unsupervised experiment in bacteriophage therapy has been in progress in the same area in Middle East in which the investigations to be recorded later in this communication were carried out, and it has been possible to obtain accurate data which are of considerable interest.

The test population is provided by the inmates of an internec camp where male enemy aliens mainly of Italian nationality are detained. This camp is run under British military supervision on much the same lines as a prisoner-of-war camp but has greater amenities. Among other privileges the internees are allowed to receive visitors, and at stated intervals wives and other relatives arrive, bringing with them gifts which have to be "declared". The favoured gifts are flowers, fruit, sweets, books, and in the same category of importance (mute witness to the local faith) bacteriophage. It is improbable that its use is universal but it is a fact that large quantities of bacteriophage are imported and taken both prophylactically and as treatment.

A few miles away in identical surroundings and under the same sanitary supervision, is an Italian prisoner-of-war camp where bacteriophage is unknown.

Accurate records are maintained of cases of clinical bacillary dysentery with typical blood and mucus admitted to hospital from both camps, in each of which the numbers at risk run into thousands. The rate of admissions per 1 000 in a period of four months is shown in Table I.

TABLE I  
RATE PER 1 000 OF ADMISSIONS TO HOSPITAL FOR CLINICAL DYSENTERY

	Internee Camp (Phage used.)	P.O.W. Camp (No phage)
May	3.5*	3.19
June	8.28	2.47
July	4.88	1.60
August	3.32	1.42

The bacteriophage in question is of course one or other of the local products which are for sale in most chemist shops in these parts. The beneficial results of its use are not apparent in these figures.

## SCHEME OF THE PRESENT INVESTIGATION

Bacteriophage was, according to the statements of German medical officers the standard treatment for bacillary dysentery in the forward troops of the German Army in Africa. The preparation used is Ruhr-Bakteriophagen, Polyvalent, Behringwerke and carries the Bayer trade mark. It is elegantly put up in special brown glass bottles with rubber stoppers and viscag in

volumes varying from 50 c.c. to 500 c.c. Large quantities of this bacteriophage were captured during the Axis retreat from El Alamein.

It was decided to use Ruhr Bakteriophagen in the treatment of cases of bacillary dysentery occurring among certain German prisoners of war but to restrict it to one half of the community and to place the other half on standard non bacteriophage treatment, thus obtaining comparative figures from which the value of bacteriophage treatment might be assessed.

Camps in which prisoners of war are incarcerated are divided up into sections or cages which are more or less identical. These are equipped to take the same number of men in well-spaced tents, they have the same amenities, the same cooking arrangements and food, and the same sanitary arrangements. The population is relatively stable, and the inmates of the various cages do not mix to any extent. The standard of health and freedom from epidemic diseases compares favourably with that of any other community in Middle East.

The medical arrangements are alike in all cages. Each has its medical officer (a German prisoner of war) and Medical Inspection Room. Trivial cases of all kinds are treated "in quarters." Patients who are sufficiently ill to require special attention are removed from the cage and admitted to a very well equipped camp hospital, from which, if the condition is serious or if the patient is likely to be ill for some time they are transferred to a large prisoner of war hospital which forms a section of a British General Hospital. This prisoner-of-war hospital is staffed by German medical officers, but is administered by the staff of the British General Hospital and supervised by its specialists. Dysentery cases with blood and mucus are first admitted to the camp hospital, but are invariably passed on to the other as soon as possible.

In the prisoner-of-war camp selected for the trial, two separate but strictly comparable communities were created by a random grouping of cages into two series. Dysentery cases from one series received bacteriophage treatment, those from the other did not. A further cage was set aside for a small experiment in prophylaxis.

Throughout the trial the patients were under the charge of their usual medical officers and, except for the special instructions given in respect of the bacteriophage therapy no change was made in the normal routine of medical treatment employed by the German medical officers. In the main hospital all cases were attended by one officer who remained unchanged throughout the trial.

The bacteriological examination of specimens from patients was carried out in a Mobile Bacteriological Laboratory under the charge of one of the authors (B. P.), who also held a watching brief over the progress of the cases and the maintenance of statistical records. The typing of the Flexner strains, the titration of the bacteriophages, and other similar tests were carried out in the Central Pathology Laboratory.

The main experiment was continued over a period of two months from

10th May to 9th July. Although this is a season in which cases of bacillary dysentery are usually common the incidence on this particular occasion was low. Nevertheless the numbers which occurred are sufficient to be significant.

### OBJECTS OF THE INVESTIGATION

The objects of the investigation were —

- (1) To determine if bacteriophage has any prophylactic action. This was carried out as a small independent experiment.
- (2) To determine if the administration of bacteriophage in the early stages of bacillary dysentery will abort the disease, i.e. reduce the number of cases which require admission to hospital.
- (3) To determine if bacteriophage therapy will modify the course of the disease and reduce the length of time which the patient remains in hospital.
- (4) To study by laboratory methods certain aspects of bacteriophage therapy.

### PRELIMINARY CONSIDERATIONS

#### (a) *Potency of Ruhr-Bakteriophagen*

Tests of the potency of Ruhr Bakteriophagen were made by the patch technique elaborated by CRAIGIE and YEN (1938) for the investigation of *V1* strains of *Bact. typhosum*. 'Ten times' dilutions of bacteriophage were used, without intermediate dilutions as accurate end-points were not considered essential. The figures recorded are the highest dilution producing a clear window of lysis in a patch of culture.

- (i) The potency of Ruhr Bakteriophagen was tested against stock cultures of dysentery bacilli, typhoid paratyphoid bacilli, and a recently isolated strain of *B. coli*. Parallel titrations were made with a French bacteriophage sponsored by D. HERELLE, and with an Alexandrian bacteriophage. The results are shown in Table II.

It will be seen that Ruhr Bakteriophagen is of high potency and wide polyvalency. In both these respects it is superior to the French and the Alexandrian preparations.

- (ii) The potency of Ruhr Bakteriophagen was tested against all strains isolated in the course of the investigation with the exception of two which were accidentally lost. For convenience only a 1/1000 dilution of the bacteriophage was used. The results are recorded in Table III. All strains tested were found to be susceptible, the majority highly susceptible to the action of this bacteriophage.

#### (b) *Powers of Resistance of Ruhr Bakteriophagen*

To determine if bacteriophage remained potent and was unaffected by its passage through the stomach and bowel the faeces of a number of patients under treatment with this preparation were examined.

TABLE II  
..... RADIATION EFFECTS ON B CELLS

TABLE III  
ACTION OF RUER-BACTERIOPHAGES DILUTED 1/1000 ON STRAINS ISOLATED IN THE COURSE OF THE INVESTIGATION

	Isolations from Test Series.					Isolations from Control Series.					Total				
	C	C—	SCP	P	Nil	C	C—	SCP	P	Nil	C	C—	SCP	P	Nil
<i>B. dysenteriae</i> Shiga	13	—	—	1	—	12	5	—	1	—	25	5	—	2	—
" para-Shiga (?)	1	—	—	—	—	—	—	—	—	—	1	—	—	—	—
Schmitz	4	—	—	4	—	4	—	—	—	—	8	—	—	1	2
Sonne	—	—	—	—	—	—	—	—	—	—	4	—	—	—	—
Flex I	50	2	2	1	—	14	2	2	—	—	34	4	1	1	—
" II	4	1	2	—	—	6	1	—	—	—	10	2	2	—	—
" III	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
" IV	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
" V	7	1	—	—	—	0	—	1	—	—	16	1	—	—	1
(unclass.)	1	1	—	1	—	1	—	—	—	—	2	1	—	—	—
Total	50	5	5	7	2	50	0	3	1	1	100	14	0	8	2

Notes.—1. C = complete lysis. C— = almost complete a few tags left. SCP = semi-confluent plaques. P = plaques.  
2. Of the strains shown in the Nil column two cultures of *B. dysenteriae* Schmitz were accidentally discarded before being tested against more concentrated bacteriophage. The strain of *B. dysenteriae* Flex IV was susceptible to a 1 in 10 dilution.

TABLE IV  
PROPHYLACTIC ACTION OF BACTERIOPHAGE

	Control Cages (No Bacteriophage)				Cage on 3 Days Prophylactic Bacteriophage			
	Average Strength	Dysentery Admissions.	Rate per 1000	Rate per 1000 over 4 Weeks	Average strength	Dysentery Admissions	Rate per 1000	Rate per 1000 over 4 Weeks.
—1 week	2119	7	3.31	11.35	672	2	2.98	7.58
—2	2081	10	4.8		678	4	5.80	
—3	105	5	3.37		701	6	8.56	
—4	167	—	0.0		707	7	9.0	
3 days prophylactic bacteriophage					—	Nil	—	—
1 week	2103	7	3.10	10.50	705	3	1.25	10.5
"	2204	3	1.36		751	1	5.32	
"	997	0	3.82		811	1	4.03	
"	2251	1	1.77		812	1	4.03	



## 2. EFFECT OF BACTERIOPHAGE IN ABORTING BACILLARY DYSENTERY

In Table V the figures relating to this aspect of the investigation are given. The salient points to be noted are —

- (a) The numbers at risk are considerable.
- (b) The numbers reporting sick in the test series are higher than in the control series. This may be explained by the fact that medical officers and orderlies in the cages selected for bacteriophage treatment were instructed to be on the look out for cases of diarrhoea so that treatment could be started at the earliest moment. It seems probable that, in following these injunctions, cases were included in the series which would have passed unnoticed in the control cages where normal procedure was in vogue.
- (c) The percentage of men who developed clinical dysentery and were admitted to hospital is almost identical in both the control and the bacteriophage-treated groups, *i.e.*, 2.98 and 3.1 respectively.
- (d) It would therefore appear that bacteriophage, even when administered in large doses at the earliest symptom, is incapable of aborting an attack of bacillary dysentery.

TABLE V

INCIDENCE OF DIARRHOEA AND CLINICAL DYSENTERY IN THE CONTROL AND TEST GROUPS,  
FROM 10TH MAY 1943, TO 9TH JULY 1943 (61 DAYS)

	Control Group	Bacteriophage Treated Group
Daily average strength of group	4,590	4,070
Total number with symptoms of diarrhoea	283	347
Percentage of number at risk who developed symptoms of diarrhoea	6.16	8.5
Number of cases of clinical dysentery admitted to hospital	138	126
Percentage of number at risk who were admitted to hospital	2.98	3.1

## 3. EFFECT OF BACTERIOPHAGE IN MODIFYING THE COURSE OF AN ATTACK OF BACILLARY DYSENTERY

An assessment was made of the severity of each case on admission to hospital while data were kept of the time taken for blood and mucus to disappear from the stools, and of the length of stay in hospital. Although these criteria give only limited information, they provide a general indication of the progress of the case of sufficient accuracy to show up any gross variations.

The results are shown in Table VI on which the following comments are made.

TABLE VI

COMPARISON OF CONTROL CASES AND BACTERIOPHAGE TREATED CASES. (CLINICAL DYSENTERY)

	Control Group	Bacteriophage treated Group
Number of cases analysed	126	124
Assessment of severity on admission		
Percentage mild	75.4	83.74
" moderate	18.2	12.90
" severe	6.35	3.36
Average number of days for blood and mucus to disappear	9.03	9.03
Average stay in hospital (days)	19.83	16.97

(a) *Number of Cases*

The seven cases placed on sulphonamide treatment are excluded for obvious reasons, as are also six others regarding whom adequate data are not available. Yet another case proved to be a mixed infection of bacillary and amoebic dysentery. Two cases among medical personnel not included in Table VI because they were not inmates of the cages under observation are included in the bacteriophage treated group in Table VII.

(b) *Severity on Admission.*

The degree of severity was assessed on the condition of the patient at the time of admission. The number of stools, amount of blood and mucus, temperature and pulse rate and the general appearance of the patient were taken into consideration.

The difference between the cases in the two series was not striking but the balance was slightly in favour of the bacteriophage-treated group. This may have been due to the action of the bacteriophage already administered, but in view of the fact that living organisms were readily recovered from the stools at this stage such an explanation must be accepted with caution. In fact, the difference was more marked in the early stages of the investigation, and became less noticeable as the number of cases in both series increased. It is possible that it would have disappeared completely if the investigation had been sufficiently extended.

(c) *Average number of days taken for Blood and Mucus to disappear from the Stools and Average Stay in Hospital*

Figures for all cases of clinical bacillary dysentery are in Table VI, and grouped according to the infecting organism in Table VII.

The over all average time before blood and mucus disappeared from the stools was very similar in both series. When analyzed according to the infecting organism it is seen that there is little difference in Flexner infections, but a

TABLE VII

ANALYSIS OF ISOLATIONS OF DYSENTERY BACILLI SHOWING AVERAGE TIME FOR BLOOD AND MUCUS TO DISAPPEAR, AND LENGTH OF STAY IN HOSPITAL.

	Control Series			Bacteriophage Series		
	Number of Cases	Average Days till B/M Negative	Average Days in Hospital	Number of Cases	Average Days till B/M Negative	Average Days in Hospital
<i>B. dysenteriae</i>						
Flexner	39	8.84	19	43	8.9	17.47
Shiga	20	17.25	28.5	14	14.60	23.0
Schmitz	5	12.0	— 0	10	6	14.7
Soerine	4	3.0	20.0	—	—	—
Non-examined remainder	—	—	—	1	8.0	16.0

slight balance in favour of bacteriophage treated cases in Shiga infection. The numbers involved in the other groups are too small to be of significance.

In Table VIII an assessment is made of the same particulars in those cases in which bacteriophage action was observed in the colonies on the original plate from which the organism was isolated. Presumably these are cases in which much bacteriophage was present. The averages in this group (admittedly open to criticism because the numbers are small) show no significant variation from the averages in the control series.

TABLE VIII

ANALYSIS OF CASES IN WHICH BACTERIOPHAGE ACTION WAS NOTED IN THE COLONIES ON THE MCCOY KEY PLATE.

Type	Number of Cases	Series	Average Number of Days until Blood and Mucus Negative	Average Number of Days in Hospital
Flexner	7	Mild	9.4	19.3
Shiga	4		17.5	27.8
Schmitz	2		6.5	18.0

The average stay in hospital was less in the bacteriophage-treated cases than in the controls. A noteworthy feature is the undue length of this period in both series. It is considerably greater than is found necessary in British hospitals, and under British medical officers.

To summarize, it may be said that bacteriophage treatment produced no dramatic results in modifying the severity or duration of the attack. The slight balance in favour of the bacteriophage group might well have been levelled out in the course of a more extended observation.

#### LABORATORY ASPECTS OF BACTERIOPHAGE THERAPY

##### (a) Effect of Bacteriophage on the Isolation of Dysentery Bacilli from Faeces

The isolations of dysentery bacilli, details of which are in Table II, were disappointingly low. Specimens were selected by the German medical officers or orderlies placed in small vials of glycerine saline solution, and sent to the laboratory for plating. The laboratory was some little distance outside the hospital enclosure, and it was not feasible to send freshly passed stools in the bedpan. The isolation rate is considerably lower than that obtained by the same laboratory from outlying British units (78 per cent.) where a similar technique was used. The most probable explanation is that sufficient care was not exercised by the German personnel in the collection of suitable fresh specimens.

The percentage of isolations is very similar in both series—50 per cent. in the control and 55.5 per cent. in the bacteriophage treated series. It has already been shown that bacteriophage is present in the faeces of treated cases on the morning following its exhibition and persists throughout the treatment. Table IX shows the days on which isolations of dysentery bacilli were obtained. It will be seen that the presence of bacteriophage in the faeces did not appear to lessen the chances of isolating the dysentery bacillus, despite the fact that *in vitro* the strains were found to be susceptible to its action.

TABLE IX.

DAY ON WHICH DYSENTERY BACILLI WERE ISOLATED FROM THE STOOLS.

Series	Number of Cases in which Dysentery Bacilli were first isolated on			
	Day of Admission to Hospital	Day following Admission to Hospital.	2nd Day following Admission to Hospital.	3rd Day following Admission to Hospital.
Control series	31	32	4	1
Bacteriophage series	19	41	9	1

Note—1. The days in the Table are those on which the specimen was passed.

2. Bacteriophage was always given on the day of admission, and may have been given 1 or 2 days earlier.

*(b) Further Experiments*

Further experiments were carried out to obtain more specific data on some of these points.

A healthy volunteer swallowed 2 doses of 50 c.c. of Ruhr Bakteriophagen at an interval of 12 hours. Bacteriophage was present in his stools the next morning and remained in diminishing concentration for 6 days, after which it could not be detected by the technique detailed above.

The same volunteer on a subsequent occasion swallowed 100 c.c. of bacteriophage, and 6 hours later a specimen of blood was taken. Bacteriophage was present in the serum in a concentration which, using the patch technique gave complete lysis in a dilution of 1 in 1000.

Specimens of urine were examined after 3 6 9 and 24 hours. Bacteriophage was absent from the 3 hours specimen, present in the 6 hours specimen, and absent from all later specimens.

Another volunteer repeated this experiment with the following results —

Hours		Serum contained bacteriophage giving	
After		complete lysis	
3		in a dilution of 1/100	
6		"	1/1000
14		"	1/10
24		Not demonstrable.	

Thus it would appear that when bacteriophage is swallowed some of it is quickly absorbed and reaches its highest level in the blood in about 6 hours. Within 24 hours it is no longer to be detected in the blood having been excreted and possibly in part destroyed by the tissues.

It is present in the stools on the morning after administration and persists for at least 6 days.

Five mild cases of bacillary dysentery in a British hospital were selected and treated for 3 days with 15 c.c. of Ruhr Bakteriophagen three times daily. The stools were examined repeatedly for the presence of bacteriophage and dysentery bacilli, and the serum was tested for bacteriophage 24 48 and 120 hours after the beginning of treatment.

The results are shown in the diagram. They illustrate the persistence of bacteriophage in the stools, and the simultaneous presence of dysentery bacilli. In Cases 1 2 and 5 the infecting organism was recovered after bacteriophage had been present in the bowel for 4 days, in Case 3 after 2 days, and in Case 4 after 1 day. All the organisms were readily susceptible to the action of the bacteriophage.

It is noteworthy that bacteriophage persisted as long in the stools of the normal volunteer as it did in the stools of patients suffering from bacillary dysentery. There is thus nothing to suggest multiplication of the bacteriophage in the presence of its specific *parabulum* in the bowel.

ISOLATION OF DYSENTERY BACILLI IN RELATION TO PRESENCE OF BACTERIOPHAGE IN THE BODY

Case Number and Type of Organism.	Day of Disease									
	1	2	3	4	5	6	7	8	9	10
1 Flexner Type I										
2 Flexner Type I			+	+	+					
3 Flexner Type V										
4 Flexner Type II			+	+						
5 Flexner Type V										

= Bacteriophage 15 a.c. t.d.s. by mouth.  
 = Bacteriophage present in stool.  
 = Bacteriophage content of stool not tested but shown by previous experiments to be invariably present at this stage  
 + = Organism isolated from stool  
 - = Bacteriophage present or absent in blood stream.

dysentery organisms isolated. It was recovered from the stools of patients to whom it was administered.

3 No prophylactic action was found to result from a 3-day administration of bacteriophage along the lines recommended by KLEWER and HELLMERICH.

4 The incidence of dysentery in a community treated with bacteriophage at the first sign of diarrhoea was no different from that in a control community.

5 Neither the severity nor the duration of the attack in the bacteriophage-treated group was dramatically less than in the controls.

6 Dysentery bacilli were recovered from the stools after the bowel had been exposed for as long as 4 days to the action of bacteriophage.

7 It is concluded that bacteriophage fails to exercise *in vivo* the potent properties which it exhibits *in vitro*.

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#### REFERENCES

- COSTA CRUZ (1924) *C. R. Soc. Biol. Paris* 81 845  
 CHRODERURY B. K. P. & MORRISON J. (1929) *Indian med. Gaz.* 64 66  
 COMPTON A. (1928) *J. infect. Dis.* 43 448.  
 — (1929) *Lancet* 2 273  
 — (1942) *Brit. med. J.* 1 719  
 CRAIGIE, J. & CHUN HUI YEN (1938) *Canad. publ. Hlth J.* 29 448 484  
 DAVISON W. C. (1922) *Amer. J. Dis. Child.* 23 531  
 GUTHRIE O. (1941) *Deutsch. med. Wschr.* 67 578  
 HALLER, D. (1933) *Brit. med. J.* 2 863  
 HESLER, C. (1943) *Med. Welt* 3 60  
 D'HOMELLE, F. (1926) *The Bacteriophage and its Behavior*. English translation. London: Baillière, Tindall & Cox. Baltimore: Williams & Williams Company.  
 JOHNSTON M. M., EBER, J. H. & HAARS, M. J. (1933) *Canad. Publ. Hlth J.*, 24 443  
 KIDDER, J. F. & ROSE, E. J. (1933) *Ann. intern. med.* 6, 1193  
 KLEWER, H. & HELLMERICH, W. (1941) *Deutsch. med. Wschr.* 66 617  
 MCCAY F. H. (1934) *S. Af. med. J.* 2 721  
 MURRAY J. E. (1938) *Practitioner* 141 199  
 OUBRAVOAL DES EMBARTS, J. (1933) *Bull. Soc. Path. Exot.* 26 979  
 RIDING, D. (1930) *J. Hyg. Camb.* 30 387  
 SPENCER, R. C. & MCKINLEY E. B. (1924) *Sth. med. J.* 17 538  
 SOEDMAN J. (1941) *German. Typhus. Ned. Ind.* 61, 1963  
 TAYLOR, J., GRIFFAL, S. D. S. & TRANT V. (1930) *Indian J. med. Res.* 18 117  
 TORLEY W. W. C. & WILSON J. (1925) *J. Hyg. Camb.* 24 285  
 — — — — — & LEWIS, E. R. (1925) *Ibid.* 24 17  
 VALL, S. & MORTON G. L. (1937) *J. Lab. clin. Med.* 22 594  
 WHITLER, K. M. & BURDORF A. L. (1941) *Amer. J. Publ. Hlth*, 31 325

## SEROLOGICAL EXAMINATION AND A CUTANEOUS TEST IN THE DIAGNOSIS OF BACILLARY DYSENTERY

BY

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Considerable difficulties exist with regard to the laboratory diagnosis of bacillary dysentery. Their source is commonly known to be the outstanding sensitivity of the bacilli to environmental conditions: their brief viability when exposed to light, cold, traces of urine or disinfectants, especially in stools where the presence of bacteriophage represents a continuous danger to their existence. Thus the time passing until cultivation is performed, the distance of the laboratory, the choice of suitable portions of the dysenteric stool, the climatic conditions are some of the factors which may influence the result of the bacteriological examination. Attention has therefore been paid to obtaining the specimens at the patient's bedside and culturing them at once. By taking dysenteric exudate directly from the bowel by a rectal swab or by rectoscopy positive results are more frequently obtained. Nevertheless the difficulties are still great, especially in cases of chronic bacillary dysentery where the percentage of negative cultures is notoriously large. In ROGERS's (1929) opinion a positive culture is exceptional in those cases. Therefore a number of diseases of the bowels caused by chronic dysenteric infections are certainly misdiagnosed for lack of confirming bacteriological evidence.

Also the clinical diagnosis of dysenteric disorders has its fallacies, indeed more in chronic than in acute dysentery. Acute bacillary dysentery it is true, is generally diagnosed as such and not commonly confounded with other acute diseases of the gastro-intestinal tract. Chronic bacillary dysentery on the other hand, represents a difficult problem especially because of its protean nature simulating very different diseases of the intestine.

The exact diagnosis of bacillary dysentery however is of definite importance since modern chemotherapy particularly sulphaguanidine and, to a



certain extent, vaccino-therapy are very efficient in the treatment of those cases and, as we are inclined to assume, only of those cases. As are the results of specific chemotherapy spectacular in suitable cases so are they poor in other dysenteriform conditions of the bowels.

It is evident, therefore that the diagnosis of bacillary dysentery should be improved by all available means. The search for additional diagnostic procedures led to the use of the agglutination test especially in cases of long duration. The finding of agglutinins does not seem to be so constant in the serum of patients ill with bacillary dysentery as it is in other infectious diseases, a fact which may be explained by the lack of bacteraemia in this disease compared, for example with the enteric fever group or brucellosis. A survey of the literature on the subject reveals different opinions concerning the diagnostic value of these agglutinins. MANSON-BARR (1939) and BOYD (1940) are somewhat sceptical about the evaluation of this examination—the former calling it an “unstable weapon” in bacillary dysentery and stressing the finding of agglutinins in some normal sera. BOYD points out the difficulties encountered because of the diversity of the paratyphoid organisms and describes an elaborate technique to avoid pitfalls in serological diagnosis. MANSON-BARR describes the behaviour of agglutinins: he appreciates a positive finding particularly in the detection of carriers and, in a recent article, emphasizes its usefulness in the diagnosis of chronic cases. He regards a titre of 1/40 as diagnostic for Shiga infection and of 1/100 for the paratyphoid group. TORLEY and WILSON (1934) think that complete reliance should not be placed on the demonstration of agglutinins in the diagnosis of dysentery. A titre of 1/40 is highly suggestive of a Shiga infection while a titre of 1/150 for Flexner in the absence of Shiga and typhoid agglutinins is suggestive of a Flexner infection, this being partly confirmed by a rise and fall in the agglutinin curve. Agglutinins are said to decline shortly after convalescence and to disappear within three months after infection except in cases of chronic carriers where they may persist for much longer. CRICKERHANK and SWYER (1940) mention the serological examination as an aid which proved to be valuable in an outbreak of Sonne dysentery. MUEHLERS ROSE and ZUR WERTH (1930) quote the opinions of several authors who deny any value in this method, whereas they themselves consider the examination as a method which can be used to advantage especially in differential diagnosis against amoebic dysentery. SCHITTENHELM (1925) gives about the same diagnostic titres as MANSON-BARR (1942): he even compares its usefulness with that in typhoid, when used with the necessary caution. BLATT and SHAW (1938) in a survey of bacillary dysentery in children, felt that the procedure probably was reliable and should be tried further.

We have used the agglutinin determination in twenty five bacillary dysentery patients acute and chronic, and in forty three control cases with various dysentery like and other diseases. We have considered 1/100 and more as a

The purpose of this study is to determine the value of the skin test in the diagnosis of bacillary dysentery. The results of the study are as follows: The skin test is a reliable method of diagnosis in the majority of cases. It is especially valuable in the diagnosis of Shiga dysentery. The skin test is a simple and rapid method of diagnosis. It is a valuable addition to the routine laboratory diagnosis of bacillary dysentery.

The purpose of this study is to determine the value of the skin test in the diagnosis of bacillary dysentery. The results of the study are as follows: The skin test is a reliable method of diagnosis in the majority of cases. It is especially valuable in the diagnosis of Shiga dysentery. The skin test is a simple and rapid method of diagnosis. It is a valuable addition to the routine laboratory diagnosis of bacillary dysentery.



routine laboratory diagnosis an additional method was devised by one of us (F. D.) in the attempt to provide the clinician with another diagnostic method in bacillary dysentery (Flexner). BROOKMAN in 1921 had worked out a test for diagnosing Shiga dysentery by administering Shiga toxin intracutaneously. In a similar way to Schuck's test in diphtheria a negative reaction shows the presence of antibodies and is therefore diagnostic of previous Shiga infection. Similarly our method represents a test of cutaneous sensitivity to Flexner vaccine and a positive response is regarded as an expression of preceding

various time intervals, weeks or several months, whereas a positive cutaneous test seems to have a tendency to persist for a longer period. The agglutinins did not reach a titre higher than 1/200 in any case and frequently only 1/100 but we have frequently observed the typical rise in agglutinin titre during the course of infection (0 1/50 1/100).

In bacillary dysentery the determination of blood agglutinins and a test of cutaneous sensitivity to Flexner vaccine as described above seem to provide valuable information for the diagnosis of this condition. These examinations are indicated in cases where infection with bacillary dysentery is suspected and cannot, or can only with the utmost difficulty be confirmed by the usual means available for clinical and laboratory diagnosis. Although neither of the two tests can be compared with the certainty of the Widal-reaction in typhoid they seem to be useful when evaluated together with the clinical picture of the disease.

#### SUMMARY

The difficulties in laboratory and clinical diagnosis of bacillary dysentery and, on the other hand, the desirability of an exact diagnosis in those conditions are stressed.

A short survey of the literature of the agglutination test in bacillary dysentery is given. The behaviour of these agglutinins is briefly discussed. A method of testing the sensitivity of the skin against dysentery bacilli is described and both methods besides the usual diagnostic means applied in a mixed group of 69 cases, among them 26 of bacillary dysentery.

Both procedures seem to have proved their usefulness as aids in the diagnosis of dysenteric disorders.

#### REFERENCES

- BLATT M. L. & SHAW N. G. (1933) Bacillary dysentery in children, *Arch. Path.* **24** 216.  
 BORD I. S. H. (1940) The laboratory diagnosis of bacillary dysentery. *Trans. R. Soc. trop. Med. Hyg.* **33** 533.  
 CRUCKSHANK, R. & SWYER, R. (1940) Outbreak of Sonnei dysentery. *Lancet* **2** 803.  
 MASON BARR, P. (1939) *The Dysenteric Disorders*. London: Cassell & Co.  
 ——— (1947) Dysentery and diarrhoea in war time. *Brit. med. J.* **2** 348.  
 ROGERS, L. (1939) *Recent Advances in Tropical Medicine*. London: Churchill.  
 MÖHLING, P., ROGGE, R. & KLEIN, V. (1930) *Krankheiten und Hygiene der warmen Länder*. Leipzig: Thieme.  
 SCHÜTTENHEIM, A. (1925) *Handbuch der Inneren Medizin: Infektionskrankheiten*, **1** 581. Berlin: Springer.  
 TOPLEY W. W. C. & WILSON, G. B. (1934) *The Principles of Bacteriology and Immunity* 4th Impression. Vol. II. London: Edward Arnold & Co.

## PENTAMIDINE IN THE PREVENTION AND TREATMENT OF \* TRYPANOSOMIASIS

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### I. PENTAMIDINE IN TREATMENT

#### A. RATE OF DISAPPEARANCE OF PARASITES FROM THE PERIPHERAL BLOOD

In guineapigs infected with *Trypanosoma gambiense* and treated with a single dose of 0.002 to 0.003 gramme per kg., the time before the complete disappearance of the parasites in the peripheral blood was at least 41 hours and in some cases slightly more than 54 hours. In sleeping-sickness patients the trypanosomes were still detected 48 hours after a single dose of 0.002 gramme per kg. But, as a rule the parasites are no longer present in the blood and the gland juice on the 3rd day after this average dose.

#### B. INTERVAL OF ABSENCE OF TRYPANOSOMES FROM BLOOD AFTER SINGLE DOSES.

This experiment was made on guineapigs infected with various strains of *T. gambiense*. The date of injection was delayed for several days after the first spontaneous trypanolytic crisis that is until the disease was firmly established.

\* We are indebted to Messrs. May & Baker for adequate supplies of pentamidine (May & Baker 800) for the purpose of this investigation.

<i>Dose</i> <i>Gramme per kg</i>		<i>Dose</i> <i>Gramme per kg</i>	
0.0005	Relapse after $\pm$ 35 days	0.002	No relapse in one-third of the animals. Others relapsed after 23 to 123 days.
0.0015	" 38	0.003	No relapse in one-half of the animals. Others relapsed after 11 to 102 days.
0.001	" 13 and 91	0.005	No relapse.
0.0015	" 81		

Some of the strains used in this experiment were trypanamide-fast, but this did not impair the effectiveness of the pentamidine.

### C. CURATIVE ACTION OF REPEATED DOSES IN INFECTED GUINEAPIGS.

Various doses have been given two or three times a week, up to a total of 10 injections.

<i>Twice a week —</i> <i>10 injections of</i> <i>Gramme per kg</i>		<i>10 injections of</i> <i>G</i> <i>Gramme per kg</i>	
0.00025	Relapse after 38 days	0.0015	No relapse.
0.0005	" 15	0.002	
0.00075	No relapse.	0.003	
0.001	"	0.005	Died, poisoned, after the 7th injection.
0.00125			
<i>Three times a week —</i> <i>10 injections of</i> <i>Gramme per kg</i> 0.001 0.002			Died soon after the 10th injection.

The toxic effects of the drug are increased when the injections are made at short intervals. It seems that the dose of 0.003 gramme per kg is the largest one tolerated when repeated, and that it is advisable not to exceed two injections per week. The best results are obtained with doses of 0.001 to 0.002 gramme per kg body weight.

### D. PENTAMIDINE IN SLEEPING-SICKNESS CASES.

#### 1. Recent Infections

Only two early cases have been treated with average doses of pentamidine. One of them was clinically in perfect health.

C.S.F. three cell 0.22 0.00 albumin. Weichbrodt reaction for globulin negative. Cured with 0.95 gramme (ten injections of 0.05 to 0.1 gramme two injections weekly). The second one had a slight increase of cells in the C.S.F. eighteen cell 0.22 0.00 albumin. globulin reaction negative. He received only two injections of 0.1 gramme and three of 0.14 gramme, in all 0.67 gramme of pentamidine.

\* One of these animals, heavily infected, was given, after a relapse, one more injection of 0.003 gramme per kg and relapsed again after 12 days. This suggests the possibility that the trypanosomes might have acquired some degree of drug fastness.

For both patients this dosage had been calculated at 1 mg to 3 mg of the drug per kg body weight injected intramuscularly

The second patient presented marked symptoms of intolerance for the drug. Treatment was interrupted after the fifth injection and followed by a few injections of trypanamide and Bayer 205

Final result was the clinical cure and a normal cerebrospinal fluid ten cells 0.22 o/oo albumin globulin test negative

## 2 Advanced cases with clinical and cerebrospinal signs of encephalo-myelitis not yet treated with other drugs

### A—Injection twice weekly on an average of 1 to 2 mg per kg body weight

Case 1 S M.—C.S.F. 124 cells 0.56 o/oo albumin, globulin test = ++ Injected twice weekly 0.05 gramme,  $4 \times 0.10$  gramme intravenous and  $5 \times 0.1$  gramme intramuscular. The drug was well tolerated the clinical result not appreciable but the cell count in the lumbar fluid was better 31 cells 0.56 o/oo albumin globulin test dubious

The patient was treated later with trypanamide and antypol and she did not improve

Case 2 J B.—C.S.F. 310 cells 0.71 o/oo albumin, globulin test = ++ Same plan of treatment for a total dose of 0.96 gramme pentamidine. Lumbar puncture after this treatment 145 cells albumin increased to 0.85 o/oo globulin test still ++

A second puncture 1 month later 608 cells 0.85 o/oo albumin. Clinically worse but the trypanosomes had disappeared

Case 3 A E.—A similar case C.S.F. 110 cells, 0.4 o/oo albumin globulin test ++ Doses of 0.06 gramme 0.1 gramme (which was badly tolerated) 0.05 gramme and 0.025 gramme. These last injections provoked marked signs of intoxication. The treatment had to be interrupted, and at that time the C.S.F. showed 395 cells 0.56 o/oo albumin. No more trypanosomes in the blood and enlarged lymph glands

Case 4 A K.—C.S.F. 312 cells 1.13 o/oo albumin and many trypanosomes. Injected in the muscle twice a week 0.1 gramme of pentamidine total 1 gramme. Drug well tolerated. There was a slight clinical improvement and after this treatment, the fluid showed 130 cells, 0.85 o/oo albumin and a high positive globulin test.

Case 5 A I.—A case to be compared with the previous one. After a total of 1 gramme pentamidine the patient was still in poor condition cell-count in the C.S.F. had increased from 242 to 313 albumin unchanged at 0.56 o/oo.

Case 6 G E.—Very advanced case with 402 cells 0.7 o/oo albumin and numerous trypanosomes in the C.S.F. A course of treatment with a total dose of 1.22 grammes pentamidine did not improve either the clinical symptoms nor the C.S.F. However no more trypanosomes were observed and the albumin rate had decreased from 0.7 o/oo to 0.56 o/oo

### B—Injections at short intervals up to the limit of tolerance

Case 7 A A.—Very advanced case complicated with syphilis. Insane C.S.F. 142 cells 0.71 o/oo albumin, Weichbrodt test ++ Wassermann negative in the C.S.F. and positive in the blood. Injected daily  $22 \times 0.03$  gramme  $2 \times 0.04$  gramme  $5 \times 0.05$  gramme. This total of 0.99 grammes was fairly well tolerated. C.S.F. after treatment 85 cells 0.71 o/oo albumin, Weichbrodt ++ Clinically unchanged. Trypanosomes no longer found in the blood.

Case 8, M M.—A late case of sleeping sickness with all the classical symptoms C.S.F. 1680 cells 0.71 o/oo albumin, Weichbrodt test ++ trypanosomes present in blood and glands

Injected daily  $15 \times 0.04$  gramme  $12 \times 0.05$  gramme in all 1.2 grammes pentamidine. After this treatment, which was well tolerated and did not give later any signs of delayed intoxication, the C.S.F. showed 765 cells 0.56 o/oo albumin and numerous live

trypanosomes. However trypanosomes were no longer to be found in the blood nor in the enlarged lymph glands.

### 3. Advanced cases, formerly treated without success with various drugs

**Case 1 M. S.**—Was an advanced case with 685 cells 0.48 o/oo albumin and trypanosomes in the cerebrospinal fluid, when he received a course of 10  $\times$  2 grammes trypanamide  $8 \times 0.5$  gramme trytribine a third of 3 grammes only treparamide and 6  $\times$  0.5 gramme trytribine and finally 14 injections of 1 gramme treparamide.

He was better for a short time but relapsed clinically after 8 months and was treated with pentamidine.

Before treatment the C.S.F. showed 217 cells 0.71 o/oo albumin globulin test  $\pm$ . After 0.50 gramme 0.60 gramme 2  $\times$  0.1 gramme 0.1 gramme the cerebrospinal examination gave the following result 178 cells 0.1 o/oo albumin and globulin test  $\pm$ . No clinical improvement. Died.

**Case 2, M. K.**—C.S.F. before treatment 150 cells 0.71 o/oo albumin Weichbrodt reaction ++. After a first injection of 2 grammes treparamide the trypanosomes were still present in the blood and were considered to have a certain degree of arsenic-fastness. Therefore, the patient was treated with a considerable amount of Bayer 205 and the antimony compound trytribine. From October 1939 to May 1940 he received a total of 20 grammes Bayer 205 and 20 grammes trytribine.

The C.S.F. was still altered (89 cells, 0.56 o/oo albumin) and the following courses of trypanamide injections did not improve this or the clinical state of the patient. On 26th June 1941 lumbar puncture showed 508 cells, 0.71 o/oo albumin and a very positive globulin test.

He was then injected with 5  $\times$  0.05 gramme and 4  $\times$  0.075 gramme pentamidine without clinical improvement, but the C.S.F. was better 144 cells, 0.56 o/oo albumin.

Treatment with trypanamide Bayer 205 and antimony compounds was tried again but after 6 months the trypanosomes were still numerous in the altered cerebrospinal fluid.

**Case 3 L. K.**—On the date of diagnosis, the C.S.F. contained 220 cells, 0.71 o/oo albumin, and excessive globulin. The trypanosomes did not seem trypanamide-fast. But after 1½ years treatment with trypanamide, Bayer 205 and trytribine there was only a slight improvement. Pentamidine was then tried, when the C.S.F. still showed 59 cells, 0.4 o/oo albumin. The patient got 2  $\times$  0.03 gramme, 1  $\times$  0.06 gramme, and 7  $\times$  0.16 gramme partly intravenous, partly intramuscular. No changes in the clinical state, nor in the C.S.F.

**Case 4 F. E.**—A similar case with 250 cells, 0.85 o/oo albumin in the cerebrospinal fluid. Treated for 1 year with trypanamide, trytribine and Bayer 205. When treatment of pentamidine was started, the analysis of C.S.F. showed 57 cells 0.56 o/oo albumin and a high positive globulin test. The patient received 1  $\times$  0.06 gramme  $\sim$   $\times$  0.1 gramme intravenous, and 2  $\times$  0.1 gramme intramuscular.

No appreciable result the C.S.F. still contained 140 cells and 0.71 o/oo albumin.

Further treatment with trypanamide Bayer 205 and antimony was equally useless. Died in September 1942.

**Case 5 I. M. B.**—The combined treatment of Bayer 205 trypanamide antimony and pentamidine has given a fairly good result in this advanced case a classical sleeping-sickness case with blood infection and altered C.S.F. 267 cells 0.85 o/oo albumin and Weichbrodt ++.

The patient was injected with 6  $\times$  2 grammes trypanamide 3  $\times$  2 grammes Bayer 205 4  $\times$  0.5 gramme trytribine and pentamidine 1  $\times$  0.05 gramme, 9  $\times$  0.10 gramme. One month later the C.S.F. showed 23 cells 0.32 o/oo albumin, Weichbrodt normal.

But 6 months later the C.S.F. was nearly normal six cells, 0.22 o/oo albumin, and the condition of the patient was good.

**Case 6 Z. B.**—Advanced case insane C.S.F. 170 cells 0.4 o/oo albumin, Weichbrodt ++. The combined treatment started with 10  $\times$  2 grammes trypanamide and 7  $\times$  0.3 gramme trytribine. The C.S.F. was then distinctly improved 4 cells, 0.4 o/oo

albumin. The mental state was nearly normal. The patient then got  $1 \times 0.05$  gramme pentamidine  $1 \times 0.1$  gramme intravenous and  $8 \times 0.1$  gramme intramuscular.

He appeared to be cured. The analysis of C.S.F. after 3 months: 3.2 cells 0.22 o/oo albumin. After 9 months: 12 cells 0.22 o/oo albumin, Weichbrodt negative.

## II. PREVENTIVE ACTION OF PENTAMIDINE.

The above experiments suggested that the drug has a prolonged and cumulative action together with a slow rate of elimination or excretion. The process must be similar to that of Bayer 205 apparently forming some stable combination with proteins of the body and so maintaining the trypanocidal activity of the pentamidine over a long period.

### A. EXPERIMENTS ON GUINEAPIGS

#### 1.—*One Single Dose and Infective G. palpalis*

G.P. No. 251.—One single dose of 0.002 gramme per kg. on 19th May 1941. Infective tsetse flies were fed from 21st May to 29th July. On dissection five salivary gland positive flies were found. The animal was positive on 30th July and infected by the last batch of flies. The probable duration of protection including the incubation period was 72 days.

G.P. No. 29.—One single dose of 0.002 gramme per kg. on 13th June 1941. Infective flies were fed on the animal from July to 20th September. Eleven positive flies have been dissected in the four batches used for this experiment. The duration of the protection including incubation (average of 12 days) was 117 days.

Flies were fed every two or three days on the animals and the guineapigs were bitten by infective flies at least twice a week.

#### 2.—*One Single Dose and Positive Blood.*

Three guineapigs protected with a single dose of 0.002 gramme per kg. were inoculated once a week with blood containing numerous trypanosomes. The strain was not drug fast. Protection lasted for 69 to 115 days, this interval including the incubation period.

Four more animals, two injected with 0.002 gramme, two others with 0.003 gramme per kg. were inoculated as above, but the strain of trypanosomes was strongly trypanamide fast. One died negative, on the 115th. The survivors were protected for 21 to 107 days.

#### 3.—*Three Cumulative Doses of 0.002 Gramms at Short Intervals and Infective Flies*

One of the animals which received three doses of 0.002 gramme per kg. in 5 days was exposed to infective bites during 10 months. Fourteen batches of flies have been used and flies were fed every 2 or 3 days. Only one batch did not contain any positive fly, but the remainder contained forty-six tsetses with heavy salivary gland infections. The guineapig became positive on the 327th day and thus had been protected for 315 days.

Another guineapig treated in the same way and bitten by 32 positive flies died on the 252nd day of the test, still negative. The protective period was thus about 240 days.

#### 4.—*Three Cumulative Doses of 0.002 Gramms per kg. at Short Intervals and Repeated Inoculation of Infected Blood*

The guineapig was injected once every week with heavily infected blood from various strains. The protection given by the drug lasted 120 days (incubation period included).

### B. EXPERIMENTS ON VOLUNTEERS

Two natives submitted themselves to this experiment. Both had been free from sleeping-sickness and syphilis in the past and of any treatment that could influence the results.



Bonkumu received one single injection of 0.002 grammes per kg. on 9th August, 1941. From 11th August, 1941 to 8th August, 1942 batches of tsetse flies were fed on the volunteer every 2 or 3 days. All these batches contained at least one positive fly and the total amount of flies dissected and found infected in the salivary glands was sixty. The first trypanosomes appeared in the blood of Bonkumu in August 1942, 1 year after the protective injection.

Moya was treated on the same dates. He got a single injection of 0.003 grammes per kg. Batches of flies were fed on him at the same rate and he was stung by thirty-two tsetse flies infected in the salivary glands. This volunteer was first positive on 1st June 1942 285 days after protective treatment.

Many precautions were taken during these experiments. Blood films were examined daily from the 1st week. One month after they were first bitten by infective glossinae blood cultures were made for the first time and cultures were then made every 10 days. A total of twenty-three blood cultures were made for Moya, and of thirty for Bonkumu. The method of blood cultivation was that described by BRUTSAERT and HENARD (1936).

As it seemed possible that trypanosomiasis might develop in these volunteers without blood infection but with a direct involvement of the central nervous system the C.S.F. of Bonkumu was examined on the 6th and the 10th month of the experiment. The C.S.F. remained normal.

The volunteer Moya was the first found infected on 1st June, 1942. A thick blood film stained with Giemsa was positive. The blood culture was soon after also positive in ten test tubes inoculated on 6th June and found positive on 11th June. Laboratory-bred flies were fed on Moya from the first day of his positiveness. The cyclical transmission of his trypanosomes succeeded, but infective flies were found only in the batches fed on him on the 2nd day. For this transmission nine batches were used containing a total of 417 flies. Amongst those flies, one had a gut-only infection on the 11th day, one gut-proventriculus infection the 42nd day. All those infected or infective flies were fed on 2nd June and it is interesting to note that from the 2nd to the 17th of June the thick films were negative as well as a blood culture made on 8th June. It may be mentioned that after 3rd June the best method of diagnosis *sc.* xenodiagnosis and blood culture, failed. The C.S.F. examined on 12th June was also normal.

The volunteer Bonkumu although protected by a smaller dose of only 0.002 grammes per kg. remained negative for a longer time, in fact for a whole year after the preventive injection. The trypanosomes were seen once in the thick film on 10th August but blood cultures on the same day as well as those made on 17th August and 22nd August, were still negative. In the same period *sc.* 11th to 21st August, 1942 the parasites disappeared from the blood, but were regularly present after this date. Although flagellates were present in the peripheral blood on 20th and 22nd August, the blood cultures on the same days did not succeed. Blood cultivation was not positive until

27th August, i.e., 17 days after the first demonstration of trypanosomes in the thick film.

One cyclical transmission has also been tried on Bonkumu soon after evidence of his infection. From 10th to 27th August nine batches of clean flies (i.e. 386 flies) were fed on the patient. Infected flies were found only in the batches fed on 24th and 25th August, two gut-only infection on the 12th and 15th day six gut proventriculus-gland infections on the 18th, 28th 30th 43rd and 44th day after the infecting meal. It is noteworthy that no infection occurred in the flies fed when the patient's blood was negative on direct microscopical examination.

From the clinical point of view the first days of the illness in these volunteers showed a very peculiar picture. The scarcity of the trypanosomes the negative blood cultures and xenodiagnosis for a relatively long period demonstrate how difficult the early diagnosis would be in natives protected with pentamidine moreover the two patients had none of the symptoms observed in other volunteers and as a matter of fact no symptoms at all. Even when trypanosomes were readily found in the blood the temperature remained normal. At the spot where the flies have bitten, a superficial and painful nodule is often seen this also was absent in our patients.

Bonkumu and Moya were treated and cured with strong doses of Bayer 205. It is doubtful how their illness would have turned out if left alone. It must be remembered that natives protected by Bayer 205 prophylactic doses may show a cryptic or inapparent evolution of sleeping sickness. Pentamidine has probably similar effects.

### III. EFFECT OF PENTAMIDINE ON INFECTIVE FLIES

Three infective glossinae have been isolated from batches of flies fed on an infected *Cercocebus galentus agilis*. As in former experiments the flies were separated, each one in a box, and fed on guineapigs so that the animals gave evidence of the infective responsible fly.

*Fly 1*—Fed on a guineapig 32 hours after the animal had received 0.002 gramme per kg. This meal did not disinfect the fly which was fed on five clean guineapigs at intervals of 3 days all of them became positive after an incubation period of 13 to 21 days. The fly was killed and dissected 19 days after the medicinal meal and found heavily infected in the gut and the salivary glands.

*Fly 2*—This experiment was similar to the previous one. The result was the same.

*Fly 3*—The guineapig used for the disinfecting meal received a larger dose of 0.003 gramme per kg. of pentamidine. The fly was fed 48 hours after this injection. All clean guineapigs on which this fly was fed became positive. The fly was dissected and found infected in gut and glands more than one month after the pentamidine-blood meal.

This experiment being entirely unsuccessful, the effect was tried of feeding the flies on infected animals during the cyclical evolution of *T. gambiense*.

Number of flies	Medicinal meal	Dose Grammes per kg.	Number of infected Flies		
			Gut	Proventriculus	Glands
40	10th day	0.001	4	2	3
30	9th	0.001	1	3	18
—	12th	0.003	—	—	2
48	12th	0.003	—	—	12
48	8th	0.003	—	4	6
30	8th	0.003	—	—	7

The uninfected guineapigs bitten by these flies became positive. Control with batches of flies not fed on infected animals showed a comparable number of infected flies. The figures are the following —

Flies fed on treated animal	infected	28 per cent.
	gland infections	21 " "
Flies fed on clean animal	infected	32.5 " "
	gland infections	25.8 " "

This slight difference does not indicate a real action of the drug on the cyclical evolution of the trypanosomes in the body of the glossina.

### DISCUSSION

As far as the curative value of the drug and its toxicity is concerned our results may be compared with those obtained with animals or with patients by LOURIE and YORK (1939), LOURIE (1942), SAUNDERS (1941). There is however a difference in our appreciation of the curative activity in advanced cases. We consider that pentamidine does not reach the deep nervous lesions of the trypanosomiasis as is shown by the slight action on the alterations of the cerebrospinal fluid. Compared with say trypanamide the drug which really can clean an altered lumbar-fluid, pentamidine is disappointing. Even if there is an improvement in the cell count and the albumin and globulin rate no cure can be claimed as long as normal figures are not obtained. Therefore pentamidine should be used only when the trypanosomes are arsenic-fast or when optic neuritis is to be feared but without great hope of obtaining definite results.

In early cases, pentamidine cures easily and safely gambiense sleeping sickness. It will replace Bayer 203 in arsenic-fast cases, when a first curative dose of trypanamide fails to sterilize the peripheral blood.

But it is as a preventive that pentamidine seems to have the greatest value. As happens with Bayer 203 the drug is eliminated slowly and accumulates in the body retaining a strong trypanocidal action which prevents infection by flies as well as by mechanical transmission.

At least in the case of volunteers the drug has a lasting prophylactic action probably stronger than that of Bayer 205. The useful prophylactic dose has no toxic effect and as it appears that the drug is as effective when injected in the muscles as when injected in the veins, a mass prophylaxis of the population could be carried out easily and in a short time. A large scale trial of the product was started in 1942 in a heavily infected trypanosomiasis focus of the Kwango district in Belgian Congo and we hope to collect the first results at the end of this year.\*

Owing to the necessity of following practical lines in a mass drug prophylaxis, no attempt was made to try higher doses than 0.002 and 0.003 gramme per kg. nor repeated doses. It must be borne in mind that the success of such prophylaxis depends on the swiftness and the speed of examinations, and a summoning of the whole population and the painless treatment without toxic after effects. We surmise that every 6 months all the injected natives have to be examined again and occasionally re-injected. It is important to detect all the newcomers and to protect them as they may import new strains from the vicinity. cryptic cases may occur and will be diagnosed only by some clinical symptoms confirmed by the alteration of the cerebrospinal fluid.

It was of interest to know if pentamidine carried in the blood of protected natives would disinfect the glossinae or impair the cyclical development of the trypanosomes in flies which had fed on carriers of the disease. But it seems that the drug has no such action and we remember that in similar trials made with Bayer 205 we had to use large doses of this drug to obtain marked results.

#### SUMMARY AND CONCLUSIONS

1. Pentamidine (May and Baker 800) has a strong trypanocidal action on *T. gambiense*. This action is not impaired by the arsenic fastness of the flagellates.

2. The trypanocidal action of pentamidine has a slow start and lasts long. Sterilization of the blood is only obtained at the 3rd day after the optimal dose of about 0.001 gramme per kg. To avoid toxic effects, doses of 0.002 gramme per kg. and over must not be repeated more than twice a week. Repeated doses increase the curative action especially by accumulation of the drug in the body.

3. In the case of sleeping-sickness patients intramuscular administration of the drug is less toxic and has the same effects as by the intravenous route. The drug does not cure or improve advanced cases with marked involvement.

\* The first results 3 months after the injection of pentamidine 0.002 to 0.003 gramme per kg. are promising. Not a single new case was found amongst the protected natives. Among the natives used as controls 2.5 per cent. of new infections were discovered. The experiment took place in a few villages with a total of more or less 500 inhabitants half of them being protected.

of the central nervous system. It is however useful in early cases, and is advocated when the trypanosome is resistant to other drugs, such as tryparsamide or similar arsenical compounds.

4 Flies fed on animals injected with average doses of pentamidine are not disinfected of their trypanosomes, nor is the cyclical development of their trypanosome infection influenced.

5 Evidence is adduced of the prophylactic value of pentamidine. Guinea-pigs are better protected by three doses of 0.002 gramme per kg. and were free from infection for at least 120 days. Volunteers injected with a single dose of 0.002 or 0.003 gramme per kg. resisted for 10 to 12 months repeated bites of infective tsetse flies.

#### REFERENCES

- LOURIE, E. M. & YONKE, W. (1939). Studies in Chemotherapy. XXI. The trypanocidal action of certain aromatic diamidines. *Ann. trop. Med. Parasit.* **33** 289-304.  
——— (1942). Treatment of sleeping-sickness in Sierra-Leone. *Ibid.* **36**, 113-131.  
SAUNDERS, G. F. T. (1941). Preliminary report on the treatment of sleeping sickness by 4:4 diamidino diphenoxy pentane. *Ibid.* **35** 166-174.

## THE SICKLING PHENOMENON IN THE BLOOD OF WEST AFRICAN NATIVES

BY

R WINSTON EVANS B.Sc. M.R.C.S. L.R.C.P.

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Since HERRICK (1910) first pointed out the association of sickle-shaped erythrocytes with a severe anaemia, a considerable volume of literature has appeared, especially in recent years, on one or other feature of the sickling phenomenon. Most of this literature has emanated from the Western Hemisphere and is based on observations made on American negroes. This paper gives an account of investigations and observations which were carried out on West African natives, and mainly directed to a determination of the incidence of the sickle-cell trait.

Although the American negro population was originally derived from West Africa very few cases of sickle-cell anaemia have been reported from these colonies and no account of the incidence of the sickle-cell trait in West African natives can be found in the literature apart from the work of E. C. SMITH (1934)

\* I wish to thank Lt.-Col. J. C. LEEDHAM GREEN R.A.M.C. and Lt.-Col. W. M. MACNAUGHT R.A.M.C. for much encouragement and for allowing me to refer to the patients and notes of the surgical and medical divisions.

I am grateful to Brig. R. A. HEPPLE, O.B.E. M.C. D.D.M.S. West Africa and Brig. G. M. FINDLAY O.B.E. Consultant in Tropical Medicine West Africa Force for their encouragement and interest in this communication

The incidence of the sickle-cell trait was investigated in a group of nearly 600 men, constituting natives from the Gambia, the Gold Coast, Nigeria, and the Cameroons. They consisted of a large percentage of all hospital admissions during a period of over 6 months, together with a smaller group of fit soldiers employed on hospital and other duties. The incidence of the trait among the natives of one Gambian village the population of which was mainly derived from one family (*Bojang*), was also determined.

#### TECHNIQUE.

(a) *The Moist Preparation Method*—A drop of capillary blood was placed on a clean dry slide and a coverslip was put over it. The edges were sealed immediately with vaseline and the preparation kept at room temperature and examined at intervals up to 36 hours.

(b) *The Test tube Method*—This is a modification of the method described by Beck and Hertz (1935). Approximately 2 c.c. of venous blood was placed in a 3.8 per cent citrate solution contained in a test tube 6 inches by  $\frac{1}{8}$  inch under a layer of liquid paraffin. Formaldehyde, 10 per cent. solution in saline, was then added beneath the oil after 24 hours had elapsed. After allowing 30 minutes for cell fixation moist preparations of the fixed cell suspensions were then examined.

(c) *The Small Test-tube Method of Beck and Hertz (1935).*—A drop of blood from a finger was allowed to fall into a citrate solution in a Wasmermann tube and a layer of liquid paraffin added. Formaldehyde was then used as in (b) to fix the cells after 24 hours. The fixed cell suspension was then examined.

Stains as a preliminary procedure was not employed in any of the above methods.

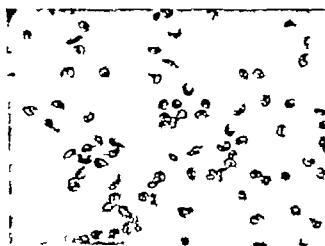
Tests for the sickle-cell trait were also made on "blood" obtained by sternal bone marrow puncture.

Although the test tube method (c) is described as a very delicate test, no significant difference in the results from those obtained when using methods (a) and (b) was found. The test tube method (b) was found particularly useful when cells fixed in the sickle form were required for demonstration or for permanent preparations.

Tests for sickling *in vivo* were made by collecting venous blood into a paraffined syringe and placing the blood immediately into 10 per cent. formal saline under liquid paraffin.

In a few instances the vital dye method of HANSEN PRUSS (1937) was used. An alcoholic solution of brilliant cresyl blue, a 1 per cent. solution in 95 per cent. alcohol, was spread on a clean dry slide and allowed to dry in a dust free atmosphere. A drop of capillary blood was then placed on the slide and a coverslip put over it. The edges were immediately sealed with vaseline and the preparation examined at intervals up to 36 hours. It was interesting to find that the brilliant cresyl blue inhibited the formation of sickle-cells, an

effect first described by DIGGS and PETTIT (1940) In one case (90 per cent of whose red blood cells were known to sickle within 15 minutes of preparation of a sealed moist blood specimen) who was retested using cresyl blue filmed slides no sickling was found to have occurred after 6 hours and only 15 per cent of the red cells had assumed the sickle form after 12 hours. This method was found useful in tracing the changes occurring in the erythrocytes during the process of sickling on account of the slowing down of the rate at which the cells assumed the sickle form. HAHN and GILLESPIE (1927) studied the characteristics of sickle-shaped erythrocytes and like them it was found that at first the cells expand and assume a spheroidal form, just as they do in the first stage of saline haemolysis. Transformation into the multi pointed sickle



CLASSICAL SICKLE-CELLS  
Formalin-fixed preparation

forms then occurs slowly In capillary blood preparations it was noted that the reticulocytes took a longer time to sickle than mature erythrocytes

#### GROUP I WEST AFRICAN SOLDIERS

In this group 561 soldiers were examined and 19.9 per cent. were found to have erythrocytes which sickled *in vitro* This group consisted of 362 natives from Nigeria and the Cameroons 18.75 per cent. of whom sickled 132 natives from the Gold Coast, 16.6 per cent. of whom sickled, and 67 natives from the Gambia 28.3 per cent. of whom possessed the sickle-cell trait.

It may therefore be assumed that 20 per cent. represents the incidence of the sickle-cell trait in a group of British West African male natives chosen at random. This figure is nearly three times as high as that found by COOLEY and LEE in their examination of 400 American coloured patients, 7.5 per cent. of whom were found to possess the sickle-cell trait. This figure obtained by COOLEY





and LEE for American negroes has been corroborated by JOSEPHS (1928), who obtained a result of 5 to 7 per cent, and other workers. The highest figure for any one group in this series was found among the Gambian natives (28.3 per cent.) and included six cases of sickle-cell anaemia, of which four died. It is realised that this high figure for Gambian soldiers may be due to the relatively small number examined and to the high rate of inbreeding.

FINDLAY (personal communication) has recently examined a random group of 300 soldiers from the Gold Coast and found the incidence of sickling to be 15.5 per cent.

TABLE.

Number Examined.	Race.	Number Positive.	Positive Percentage.
224	Nigerians	50	22.3
138	Cameroons	21	15.2
132	Gold Coast	23	16.6
67	Gambians	19	28.3
561	All Races	112	19.9 per cent.

## GROUP II NATIVES OF A GAMBIAN VILLAGE

A small group of sixty-nine villagers of both sexes, mostly members of one large family (*Bojang*) was tested for the sickle-cell trait. The incidence of the trait in this group was found to be 18.8 per cent. Of these sixty-nine persons, forty-six were males and twenty-three were females. Although the numbers are small, it is interesting to note that 22 per cent. of the males were found to be sickling and that the blood of only 13 per cent. of the females sickled *in vitro*. One family, representing the parental first and second filial generations respectively and comprising twenty-two members was included in this group. Males contributed twelve and females ten members respectively. Blood from five males (42 per cent.) sickled; only one of the ten females showed evidence of the trait. Remembering that the trait has been shown to be inherited as a Mendelian dominant character (HUCK 1923) it is worth while pointing out that only 15 per cent. of the remaining forty-seven members were found to sickle.

Full blood counts were carried out on a number of the soldiers in Group I. The mean red cell count for those whose blood sickled *in vitro* (excluding those patients who were thought to be cases of sickle-cell anaemia) was found to be 4 100 000 red cells per c.mm. In the non-sickling class of patients a mean red cell count of 4 250 000 cells per c.mm. was recorded. Cases of nutritional anaemia, hookworm anaemia, and anaemia due to other causes were included in both the sickling and non-sickling classes.

The 561 members of Group I may be subdivided into fit soldiers (302) and those suffering from acute or chronic disease (259), and for the purpose of this investigation patients admitted into hospital on account of injuries and gonorrhoea have been included among the fit soldiers. In the class of fit soldiers the incidence of sickling was 15.5 per cent. whereas among those suffering from various diseases the incidence was 25 per cent. A further analysis of the latter subgroup revealed that the highest incidence of sickling was in a series of forty six patients admitted with respiratory diseases (lobar pneumonia, broncho-pneumonia, pulmonary tuberculosis, pleurisy and lung abscess). In this series the incidence of sickling was 28.3 per cent. No significant variation from the figure of 25 per cent. was found for any other group of diseases.

### SUMMARY

- 1 The incidence of the sickling trait in the natives of British West Africa has been examined.
- 2 The figures of 15.5 per cent for fit males and 25 per cent for males suffering from acute and chronic diseases were found.
- 3 This incidence is considerably higher than previous estimates for American negroes. The reasons for this are suggested.

### REFERENCES

- BACK, J. S. P. & HEWITT, C. S. (1935) *Amer. J. clin. Path.* **5** 323.  
 COOLIDGE, T. B. & LEE, P. (1928) *Amer. J. Dis. Child.* **22**, 334.  
 DODGE, L. W. & PETTIT, V. D. (1940) *J. Lab. clin. Med.* **25** 1106.  
 FINDLAY, G. M. (1943) *Personal Communication*.  
 HAJDU, E. V. & GILLERUP, E. B. (1927) *Arch. intern. Med.* **34** 335.  
 HAMMOND-PRITCH, O. C. (1936) *J. Lab. clin. Med.* **22** 311.  
 HEDRICK, J. B. (1910) *Arch. intern. Med.* **6** 517.  
 HUCK, J. G. (1923) *Yellow Hawk Hosp. Bull.* **34** 335.  
 JOSEPH, H. (1928) *Ibid.* **62**, 53.  
 SMITH, E. C. (1934) *Trans. R. Soc. trop. Med. Hyg.* **28** 200.

## ANNOUNCEMENTS

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### TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

The Secretaries will be glad to receive Original Papers or short Notes on suitable subjects for publication in these TRANSACTIONS if approved by the Editorial Panel

Owing to the difficulty of giving the exact date of publication of any number of the TRANSACTIONS on its cover as has been our aim in the past, it has been decided to print only the month of publication at the foot of the cover and to print the exact date of publication of the preceding number at the top of the first text page of each number. In this way any confusion which might arise owing to unavoidable delays in publication after the cover has been printed will be avoided and those who consult the TRANSACTIONS will be able to discover the exact date of publication of any paper. This is often of importance from the point of view of priority.

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### NEXT MEETING OF THE SOCIETY

The next meeting will be held at Manson House, Portland Place at 3 p.m. on Thursday 16th March 1944 when Air Commodore T. C. MORTON O.B.E. R.A.F. will read a paper on "Heat Effects in British Service Personnel in Iraq."

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### WAR DAMAGED LIBRARIES POST-WAR RESTORATION

Fellows will be rendering a service to the Society if they return to Manson House any copies of the TRANSACTIONS which they do not wish to keep after they have read them.

Paper restrictions make it impossible for the Society to build up large reserve stocks and after the war many libraries throughout the world will need copies to replace those destroyed or lost.

The Council wishes to thank those Fellows who have already responded by returning copies of the TRANSACTIONS.

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### MOVEMENTS OF FELLOWS

The following Fellows from abroad have notified the Secretaries that they are *temporarily* in the British Isles. Letters addressed to any of these care of the Royal Society of Tropical Medicine and Hygiene, Manson House, 26 Portland Place, London, W.1 can usually be forwarded to the home address.

To ensure the accuracy of this list, Fellows named below are particularly requested to advise the Secretaries when they return to their stations abroad.

BLACK S. A. B. Nigeria	HAWE, ALBERT J. Gold Coast.
BURKE, M. E. T. Assam	HUGHES WILLIAM Nigeria.
CALWELL, Capt. H. G. Tanganyika Territory	LEAH JAMES IAN Nigeria.
CANNON D. A. Nigeria.	MACDONALD Brig. GEORGE, Egypt.
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GILLESPIE, A. M. Gold Coast	NEHAUL, B. B. G. British Guiana
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## ADMISSION TO FELLOWSHIP OF THE SOCIETY

All registered medical and veterinary practitioners and others interested in scientific pursuits relating to tropical medicine, whose qualifications are deemed satisfactory by the Council, are eligible for election as Fellows of the Society.

Anyone desiring to become a candidate for Fellowship of the Society should use the special form of application at the end of this Journal.

The annual subscription payable by Fellows is one and a half guineas (£1 11s. 6d.) which becomes due in advance on the 1st of April of each year.

The TRANSACTIONS and the current YEAR BOOK of the Society are posted regularly to every Fellow whose subscription is not in arrear.

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1. Extracts from Laws of the Society: No 8 — "Either the proposer or the secondor must have personal knowledge of the candidate and vouch for him as in every respect suitable for election as a Fellow of the Society." No 24. — "Every Fellow shall pay an Annual Subscription of One-and-a-half Guinea (£1 11s. 6d.)" No 25. — "The name of a newly elected Fellow shall not be placed on the Register of Fellows nor shall he be entitled to any of the privileges of Fellowship until after his first annual subscription (£1 11s. 6d.) or composition fee (£23 12s. 6d.) shall have been paid."

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### ADVERTISEMENTS

Approved Announcements are accepted by the Council for insertion in the TRANSACTIONS due to be published on the following dates —

No. 1	June 25th.	No 4	January 25th.
No. 2	July 25th.	No 5	February 25th.
No. 3	November 25th.	No 6	March 25th.

Advertisement type area : 5 inches wide 7½ inches deep (approx )

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All communications regarding advertisements should be addressed to the Advertising Manager "



A considerable difference in the incidence of various diseases was found according to the colony of origin.

In the first place we were surprised to find such a high proportion of the patients were admitted for non-tropical respiratory diseases. Lt.-Col. MacNAUGHT and I have published in the *British Medical Journal* our findings on the incidence of chest complaints which accounted for almost a third of all medical admissions. The chief features of the pneumonia cases were the dramatic response to sulphapyridine, the low death-rate and the low complication rate. The other important non-tropical conditions were outbreaks of chickenpox, cerebrospinal fever and vaccinia.

#### CHICKENPOX

The majority of the cases of chickenpox were mild but there were a number of very severe cases in which the men were acutely ill. In these patients the distribution of the rash was more that of smallpox, with maximum lesions on the face and periphery of the limbs. In all cases, however, typical chickenpox lesions were always present on the trunk. The main importance of these outbreaks of chickenpox lay in the attacking of patients already under treatment for trypanosomiasis. These patients invariably showed a very marked deterioration in their condition, shown both clinically and by an increased cell count and protein content of the C.S.F. This resulted in longer hospitalization and, in some, eventual medical boarding out of the Army.

#### CEREBROSPINAL FEVER

Fulminating attacks were common, so that soldiers apparently in their usual health would collapse on duty and be unconscious on arrival at hospital in a matter of an hour or two. Quite a number were found dead or moribund in their huts or tents. The vast majority of these cases responded dramatically to intravenous sulphapyridine although often their condition appeared desperate. Those that died were found on postmortem examination to have an acute encephalitis in addition to meningeal infection, but suprarenal involvement was not seen. A great many of these men at no time showed typical clinical signs and neck rigidity and Kernig's sign were often absent. This was so common that a routine lumbar puncture was performed on all acutely ill patients not showing definite localizing signs, and in this way a number of cases were diagnosed that might have been missed until too late.

In all cases, fulminating or not, a rash was very rarely seen—at the most a few scattered purpuric spots. The routine treatment of cases not too severely ill to swallow was the oral administration of sulphapyridine in suspension. Two gramme doses for the first twice and then 1 gramme 4-hourly. The more severe comatose or semi-comatose cases were given intravenous sulphapyridine in doses of 1 gramme until able to swallow. No toxic effects from

sulphapyridine were met with amongst any of the patients. No sequelae were noted apart from one case which showed a relapse. This man had apparently recovered and after a few days of normal temperature again complained of headache, stiffness of neck, and showed a rise in temperature and pulse rate. Lumbar puncture revealed a turbid fluid and meningococci were isolated. The organisms were not sulphapyridine-resistant and a second course cleared up the condition completely.

#### VACCINIA.

Several dozen Cameroons troops had to be admitted to hospital following vaccination against smallpox. In addition to general malaise, pyrexia and local inflammation all these men showed joint involvement. The majority had pain, redness, swelling and limitation of movement affecting one knee. A few had involvement of an elbow or wrist. In all cases the condition cleared up completely in a few days with symptomatic treatment. This response to vaccination did not appear to be related in any way to a higher incidence in these men of yaws or sickle-cell disease.

#### TROPICAL DISEASES

The vast majority of African soldiers were found on admission to hospital to have several tropical infections and it was sometimes difficult to decide which was the actual cause of his reporting sick. A soldier might for example be admitted complaining of oedema, dyspnoea, weakness of the legs and on examination show obvious foot yaws, onchocerciasis and a moderately heavy hookworm infestation. The actual cause of his major disability might, however, be vitamin B complex deficiency. On intensive treatment with marmite, the symptoms would clear up and not all the other conditions might require treatment at all. Helminth infections being practically universal had to be ignored unless the infestation was heavy and giving rise to very definite signs and symptoms. The two main weak points in the West African appear to be the lungs and liver. The importance of chest trouble as a cause of hospitalization has already been mentioned. It was our experience that it was unusual to find a normal healthy liver at autopsy no matter from what the man had died. The majority showed some evidence of early cirrhosis even though they were under 30 years of age, and in a few cases the disease had progressed to portal obstruction. The only form of neoplasm seen in the medical wards was primary carcinoma of the liver. In two or three cases after only a few weeks of ill health the man would die with enormous new growths in the liver which also showed portal cirrhosis.

This prevalence of liver disease made *toxic hepatitis* following therapy with arsenicals and anthelmintics very common. All patients given drugs liable to affect the liver had to be very carefully watched and were always put

on to extra glucose. Jaundice was so frequent after carbon tetrachloride that the administration of this drug for the treatment of ankylostomiasis was discontinued. One otherwise apparently healthy young adult with ankylostomiasis of moderate severity died of liver necrosis following the administration of the standard treatment —

Carbon tetrachlor	2 c.c.
Ol. chenopodium	1 c.c.
Paraffin liq	30 c.c.

At postmortem he was found to have had well advanced portal cirrhosis with little liver reserve and there was acute necrosis of the remaining liver tissue.

In the European wards of the hospital *infective hepatitis* was common and similar cases occurred amongst the African patients. A diagnosis of infective hepatitis was only made in these cases, however when other conditions had been excluded (such as toxic hepatitis or amoebic hepatitis). On the whole this disease was more severe in the African and ran a longer course with a more marked icterus, and this was presumably due to their having less liver reserve. Treatment was by low fat/high carbohydrate diet as far as possible. Dieting was always very difficult as it was practically impossible to make the patients understand the importance of only taking the food given. Unless carefully watched the men would always take extra food cooked in the usual palm oil or ground nut oil stew.

Amoebic abscess was only diagnosed once but *amoebic hepatitis* was common. The usual signs and symptoms were low or moderate fever with some leucocytosis, and complaint of vague upper abdominal pain and indigestion. The liver was usually palpable and tender and a slight icterus was common. Occasionally well marked jaundice was seen. In many instances no definite history of previous dysenteric symptoms was obtained from the men. This was often doubtless due to language difficulties when dealing with men enlisted from bush villages where only a local dialect was spoken. On repeated examination of the stools, cysts or active trophozoites of *Entamoeba histolytica* were found in about half the cases before treatment was started. In the others positive findings were obtained after some days treatment with a daily dose of 1 grain emetine HCl. All the patients responded satisfactorily to a course of 10 grains of emetine hydrochlor with settling of temperature and clearing up of symptoms. In some however cysts were still present in the stools and they were given a 7-days course of E.B.I. and stovarsol, getting the full course given to African patients admitted with frank amoebic dysentery. Treatment with retention of enemata of quinoxyI was not found practicable in the African wards.

#### TRYPANOSOMIASIS.

Trypanosomiasis being endemic in the Gambia, the disease was commonly seen in the troops enlisted in the colony. Cases were also seen amongst men

from the Gold Coast who had come from a sleeping sickness district, and there were other cases of men apparently infected after reaching the colony as also occurred with a few Europeans.

*Symptoms and Signs* In no case was a patient seen showing the local changes at the site of the bite nor was such a history obtained. The men were either admitted on account of the posterior cervical glands being enlarged with or without discomfort or on account of increasing lethargy either physical or mental, and complaint of persistent headache. Often the soldiers had not reported sick but were referred to the R.M.O. by the B.N.C.O. in charge who had noticed a falling off in the man's military efficiency. Sometimes the true state of affairs was only discovered after a man had been up on charges of laziness or insubordination. The early diagnosis of the disease which was insidious, depended chiefly on the alertness of the Europeans including the R.M.O. of the man's unit. An intelligent African orderly would often spot the change in the man's mentality when a European only thought he was having one of the dumb spells which the best of the Africans are prone to show at intervals.

The finding of trypanosomes in the peripheral blood was the exception rather than the rule and diagnosis chiefly depended on gland puncture and examination of the cerebrospinal fluid. About half the cases had nervous system involvement with cells in the C.S.F. increased from 30 to 1 000 per c.mm. a positive globulin and the total protein content increased from 30 up to 80 mg per cent. The glands in most cases were soft and elastic but in the more advanced cases the glands had reached the hard fibrous stage. In the Gambia congenital bilateral ptosis was not uncommonly seen, and this gave rise to a mistaken spot diagnosis of trypanosomiasis on more than one occasion. Pyrexia was not a marked feature and no typical temperature was recognized though an irregular low fever was not uncommon. Dryness of the skin which had lost its healthy shiny appearance was seen in the more advanced cases and a few showed a transient oedema about the eyes and face. The more advanced cases might even show a masklike appearance similar to that of Parkinsonism. Cases of glandular fever were found in the European wards and often the glandular enlargement found in the Africans without any other very definite signs or symptoms was similar. The absence of typical blood changes and the finding of trypanosomes on glandular puncture, however made the diagnosis quite clear. The Paul Bunnell agglutination test was not found helpful as negative results were found in apparently definite cases of infective mono-nucleosis. Whether this was due to some error in technique when preparing the sheep cells or to its being a different virus infection we could not decide.

The technique we found most satisfactory for gland puncture was as follows —

After cleaning the skin with spirit the chosen gland was firmly anchored between the left thumb and forefinger and a perfectly dry needle was pushed

into the gland and poked around. After withdrawal the needle was engaged to a dry syringe whose plunger was half drawn back and the contents of the needle squirted carefully on to a slide. After removal of the small plug of black skin the cover slip was put on and the slide examined. Failure to remove the plug of skin gave too thick a film for satisfactory examination. Before starting treatment all the patients had a C.S.F. examination and were fully investigated by the ophthalmic specialist. The routine course of treatment consisted of intravenous injections every 5 days, starting with four doses of antrypol 1 gramme and continuing with 2 gramme doses of trypanamide. The total dosage of trypanamide depended on the cell count and protein content of the C.S.F. which was checked at intervals. The patient was also re-examined regularly by the ophthalmologist during treatment. No toxic effects from trypanamide were noted with doses up to a total of 24 grammes. In many cases visual acuity was apparently improved but this was probably due to the patients becoming more co-operative as the lethargy wore off. I have had no personal experience of treatment with pentamidine (M & B 800) which was giving very alarming reactions owing to its effect on blood pressure.

The results of treatment depended on how early the disease was diagnosed and treatment started. Cases with only lymphatic or early nervous system involvement were made fit to return to duty but more advanced cases with high C.S.F. cell counts either did not respond sufficiently or relapsed later and had to be medically boarded. The majority of African soldiers were not tradesmen and were therefore not employable unless absolutely physically fit. Patients fit to be returned to their units were kept under special observation there and sent back to hospital for review and repeat examination of their C.S.F. after some weeks.

#### TROPICAL MYOSITIS.

There were always one or two cases of tropical myositis in the medical wards. This condition was chiefly seen in the natives of the Cameroons or the Eastern provinces of Nigeria. The men were admitted to hospital with a complaint of pain and swelling in muscles usually of about 1/52 duration. The commonest situations were in the muscles of the limbs but the chest and abdominal wall muscles were also affected on occasion. Usually there was only one lesion but sometimes a man would be admitted with two or a second lesion would develop whilst in hospital. Apart from this disability the men appeared to be in reasonably good general condition and no causal factor or relationship with such conditions as filariasis, helminthiasis, or sickle-cell trait could be discovered. These cases were investigated surgically and histologically by Lt.-Col. LEEDHAM GREEN and Major EVANS, and the condition was considered to be an acute degenerative condition similar to Zonker's degeneration which might go as far as suppuration (pyomyositis) when staphylococcal bacteraemia supervened.

The clinical features were moderate pyrexia and a tender diffuse or circumscribed swelling in muscles, which might show marked heat and even fluctuation. Treatment consisted in rest, by splinting if necessary and the administration of analgesics as required. About half the cases were given a course of either sulphapyridine or sulphathiazole, but their progress did not differ materially from that of those left without chemotherapy. Too early surgical interference had to be avoided as even cases apparently showing abscess formation might subside satisfactorily. If however the temperature began to swing and a well marked leucocytosis developed, surgical drainage was required. The usual period of hospitalization for those cases resolving spontaneously was about 3 weeks and longer for those requiring drainage. One fatal case was seen with extensive abscess formation deep to the pectoral muscles from which many pints of pus were evacuated. This man was in very poor general condition when first seen and died of bronchopneumonia in spite of energetic treatment.

#### VITAMIN B COMPLEX DEFICIENCY

Patients were admitted to hospital showing signs and symptoms indicative of varying degrees of deficiency of the vitamin B complex. Deficiency disease was most often seen in new recruits enlisted from up-country bush villages and was not often seen amongst soldiers on army rations.

In some cases the cardiovascular system was chiefly affected, whilst in others nervous system lesions were more prominent and skin and tongue might also be involved. Many complained of anorexia and flatulent dyspepsia.

Usually cardiac symptoms were the most prominent and the men were admitted to hospital on account of dyspnoea, weakness and oedema. On examination there might only be oedema of the ankles or all stages up to generalized water-logging. Often the patient's appearance would suggest nephritis but albuminuria was absent or only slight. The pulse was of low tension and there was tachycardia with marked cardiac dilation. The heart sounds tended to be evenly spaced and accentuated with reduplication and systolic murmurs. The nervous system lesions usually seen were reduced or absent deep reflexes, hyperaesthesia of calf muscles and dulling of sensation over the shins. These patients often showed a positive squatting test, being unable to arise from the squatting position without assistance. The other evidences of vitamin deficiency looked for included angular stomatitis, thickening of the scrotal skin, crazy pavement appearance of the skin of the dorsum of foot and front of lower leg and atrophic glossitis.

Treatment in all cases consisted of strict rest in bed, adequate diet and large doses of marmite. It was not found necessary to administer pure vitamins in the form of thiamin, nicotinic acid or riboflavin. The accompanying anaemia was treated by large doses of iron and when necessary hookworm infestation or other infection was treated during convalescence.

## SICKLE-CELL DISEASE.

Many hundreds of cases were tested by Major R. W. EVANS for sickling and the sickle-cell trait was found in 20 per cent. by means of sealed blood preparations from a finger prick. In only a few instances, however, had the men any symptoms or disability. In cases with suggestive symptoms or signs, sickling *in vivo* in the venous blood was always looked for as well by the formal saline method under liquid paraffin. We did not find gross anaemia to be a common occurrence and in those showing anaemia there were always other factors present such as hookworm disease, chronic malaria, yaws, or nutritional deficiencies. We agree with WINTROBE that the term sickle-cell disease is preferable to sickle-cell anaemia as serious and even fatal complications may be present without the anaemia being pronounced. We saw cases with symptoms due to the thrombosis secondary to sickling suggesting acute osteomyelitis, perforated peptic ulcer, various cerebral lesions with pareses. Treatment was purely symptomatic and several at postmortem showed evidence of previous thrombosis with old infarcts in brain, spleen and bowel. The majority of cases when first seen had already reached the stage of small atrophied spleen. One man, however, with severe anaemia and haemolytic crises was considered suitable for splenectomy. The treatment was highly successful so far as the anaemia was concerned but gave rise to an unexpected complication. Following operation he had extremely severe attacks of malignant tertian malaria requiring the administration of intravenous quinine and the continuation of suppressive mepecrine indefinitely as in the European. During his malarial attacks blood smears showed the presence in the peripheral blood of malignant tertian parasites in all stages of development as is usually seen just prior to death in an overwhelming attack of cerebral malaria.

Sickle-cell disease must always be borne in mind in differential diagnosis in Africans showing indefinite cerebral symptoms, rheumatism-like pains in bones and joints, severe abdominal pain or leg ulceration. Yaws must always be first excluded. Treatment is usually not very satisfactory but correct diagnosis will prevent unnecessary operations being attempted.

## MALARIA

Being in a hyperendemic malignant tertian malaria area there was practically 100 per cent. infection of the Europeans, but the Africans had very little sickness due to malaria. It was noticed, however, that on moving from one colony to another a certain proportion were admitted to hospital with an acute malarial attack. When the Africans went down with malaria they usually had a rigor temperature up to 103° or more, and complained of severe headache. With profuse sweating temperature came to normal within 12 hours and the men were symptom-free. With these attacks parasites were usually found in large numbers in blood smears. It was usual to give a 3 days' course of treatment

only and return the men to duty. In many cases the patients' symptoms had subsided completely under mist A.P.C. before the result of the blood film had been reported.

Over a period of 1 year only two cases of chronic malarial splenomegaly with anaemia were seen. These responded to treatment with adrenaline and quinine followed by large doses of iron. No case of blackwater fever was seen in an African.

#### DYSENTERY

Second only to respiratory infections in number were the admissions for dysentery. Approximately twice as many cases had bacillary dysentery as had amoebic. None of the bacillary dysentery cases were dangerously ill and only one case of Shiga was seen.

The majority of the men were treated by sodium sulphate alone and only the more severe cases were given sulphapyridine, sulphaguanidine or succinylsulphthiazole. Only one case out of several hundred was complicated. He developed multiple arthritis which took a long time to clear up. Quite a large number of the cases of acute bacillary dysentery were found to be carriers of amoebic cysts, and required further treatment after recovery from their acute infection. Amoebic dysentery was treated by ten daily injections of 1 grain emetine hydrochloride followed by 3 grains E.B.I. and 8 grains stovarsol daily for 1 week. The men did not complain of symptoms referable to these drugs as did Europeans under similar treatment and there was often difficulty in keeping the men confined to the ward quite apart from being kept in bed. It was found quite impossible to treat Africans by means of quinoxyl retention enemata as sufficient staff was not available to keep the men in bed to retain the drug. One fatal case was seen in a man who had very extensive chronic lesions affecting the entire colon. Quite a number of cases of ciliate dysentery were seen due to infestation with *Balantidium coli*. These cases cleared up satisfactorily when treated by sod. sulph. in the routine way used for the less severe bacillary infections.

#### HELMINTHIASIS

As has already been mentioned, minor hookworm infestation was common but only small numbers of cases were admitted primarily for this condition. There were, however, three men admitted with gross anaemia and circulatory failure whose haemoglobin had fallen to below 20 per cent. and who walked into the hospital in this condition. One was given a preliminary blood transfusion and all three intensive iron therapy before the use of anthelmintics. After the use of carbon tetrachloride had been discontinued they were given oil of chenopodium only in the absence of tetrachlorethylene. Round worms and tapeworms were quite often found and successfully evacuated after starvation and administration of santonin or ext. filicis. The tapeworms were invari-



ably *Taenia saginata* and almost always the worm came away in its entirety complete with head.

#### YAWS

Yaws was naturally one of the major causes of disability amongst the African troops and large numbers had bone and joint or skin lesions. In some the yaws was the cause of admission to hospital whilst in many others yaws lesions sufficiently severe to require energetic treatment were incidental to other complaints. A special ward on the surgical side was opened for these soldiers and treatment with N.A.B. or soluta was started. Many then could be discharged and continue treatment as out patients.

#### MURINE TYPHUS

The last disease sufficiently serious and common to warrant mention is murine typhus, of which there were usually one or two cases in hospital, either in the African or more rarely in the European wards. In the African patient a rash was not typically seen and diagnosis depended on a rising titre of the Weil-Felix agglutination test. This rise in titre continued after the patients temperatures had settled and convalescence was well established. The main symptoms were headache, pain in the back, marked increasing lassitude and anorexia. Some had well marked diarrhoea and enteric fever was suspected, but with the rising titre of OX 19 there was no increasing rise in the Widal which was variable in protected individuals. The pulse-rate also was higher than would be expected in typhoid. The treatment was symptomatic and though some were seriously ill all recovered with a return to normal temperature by lysis usually after 10 days sustained temperature of about 102° F.

#### DISCUSSION

Dr G. Carmichael Low: Major MURRAY LYON in his very interesting paper does not mention syphilis or leprosy amongst the natives he had to deal with. In the old days in Uganda syphilis amongst the natives was very common—so much so that a special commission was sent out to investigate it some time after I had returned to England. There is no doubt that the African native is often a pathological museum. When doing autopsies on sleeping-sickness cases in Uganda one usually found evidence of old malaria (enlarged and pigmented spleens), dysenteric ulcerations, three or more helminthic infections, including intestinal balharzial disease and the different blood filariae. Major MURRAY LYON does not mention filariae but of course under war conditions it would not be practicable to make extended observations upon these.

Dr C. O. Chesterman: My experience of African natives was before the introduction of the sulphonamides, but in 18 years I never discovered an

empyema although the mortality from pneumonia was very high. One frequently saw septicæmic cases and meningeal infections but never an empyema.

I am interested in the statement that cases of trypanosomiasis deteriorate when they have an intercurrent attack of chickenpox. One wonders whether the virus of varicella had anything to do with the breaking down of the barriers allowing the trypanosomes to get through to the central nervous system.

Were there any cases of bilharziasis and were the cases of carcinoma of the liver in any way related to this condition?

Sir Philip Manson-Bahr said the subject of sickle-cell disease was one to which considerable attention had been drawn in the United States and comparatively few cases had been described in West Africa.\*

The main pathological lesions appeared to be the fibrosis of the spleen and changes in the liver but the occurrence of cerebral thrombosis would appear to be new.

Another point of importance in comparative medicine is the tolerance of different races to different diseases and drugs. Major MURRAY-LYONS mentioned contra indications for the use of carbon tetrachloride in Africans. Though he had given much of this to Europeans and Indians he had never had any serious concern about its effects on the liver. The native has two weak spots—the lung and the liver and one must respect these in prescribing treatment.

The other point which arouses interest is the finding of jaundice in association with amoebic hepatitis. He had only seen two instances of this in his life and on both occasions there was a suspicion that it was combined with infective hepatitis but jaundice in association with amoebic abscess of the liver appears to be very exceptional.

The other point on which he would like to comment was gland puncture. According to Kirk's method this is the most useful procedure and can be applied to infections other than trypanosomiasis and leishmaniasis. It could also be used for demonstration of *Spirochaeta pallidum* in the lymphadenitis associated with syphilis.

He considered that the present emergency was most suitable for general papers such as this.

Dr R Brunel Hawes. I have been much interested in hearing Major MURRAY LYON on our conditions in the Gambia for they resemble in some ways conditions in the East.

Carbon tetrachloride appears to be definitely dangerous to people whose diet is poor in calcium and first-class protein. I used to prohibit the use of this drug for these patients. The poor high-caste Hindu who was not taking milk was an example.

\* vide SMITH E. C. (1934) *Trans. R. Soc. trop. Med. Hyg.* 28, 209.

Our cases of cerebrospinal fever responded well to sulphapyridine. We made a suspension of broken-up tablets with gum acacia for intramuscular use and this was effective though painful.

We also had an interesting outbreak of heat exhaustion. A unit that was used to marching 30 miles a day in East Africa, returned to the West Coast, where after marching some miles through low lying plains on a day when the humidity was high some 200 Africans and a number of Europeans fell out on the line of march. In all fourteen Africans were admitted to hospital four of whom were very ill and two died. The remainder responded well to saline infusion in most cases dramatic improvement was noted after 100 or 200 c.c. had been given intravenously.

Another disease we saw in Africans was psychoneurosis, a common symptom of which was paralysis of the right arm. It was of the hysterical type and no treatment in hospital had any effect. In some cases this condition appeared to be due to a *jeju* and the patient assured us that he could be cured if he were allowed to return to his own village for appropriate native treatment. Of more interest was effort syndrome amongst West African personnel. Twelve typical cases of effort syndrome almost all in semi-educated Africans who had seen service in East Africa, were discovered and studied by Major D. L. H. GODDARD who is, I believe going to publish a paper on this subject. We had a number of patients with psychosis.

Another very common disease in the Gold Coast is guinea worm infestation. These cases were all dealt with by the surgeons who found that twisting them out on a match stick was still the best form of treatment.

For balharnias of the bladder we used subophen in preference to other forms of treatment.

Dr A. Felix asked if cases of one of the enteric fevers, especially paratyphoid A fever occurred among the local population in the area, while the troops, who presumably had been inoculated against TAB remained free from these infections. He also asked if Major MURRAY LYON could give more information about his cases of murine typhus, especially how early in the disease a significant agglutination reaction with *Proteus* OX 19 had been obtained.

The President, Sir Harold Scott. Dr STANNUS has already asked one question I had in mind. Were some of these patients with severe chickenpox described by Major MURRAY LYON cases of alastrim? The two conditions are easily confused.

Speaking of cerebrospinal fever one of the most acute cases of cerebrospinal fever that occurred in my experience was during the last war. An officer was returning home from the mess reeling from one side of the path to the other when two sergeants, thinking he was drunk, offered to take him back. To them he said, I am not drunk, but very ill. He was taken to

hospital, where he died within 36 hours. Were the meningococci typed in Major MURRAY-LYON'S cases? I know of two men, both carriers of different types of meningococci who were segregated together and in time infected each other. They each developed cerebrospinal fever caused by the type harboured by the other.

Did any of the cases of infective hepatitis referred to follow yellow fever inoculation?

I saw a great deal of tropical myositis when I was a young man and even wrote a paper on that subject. None of these cases was streptococcal in origin. There was at times very great enlargement of the muscles and rarely did they clear up without operation.

Major Murray-Lyon (in reply) Syphilis was hardly seen at all. The other venereal diseases were common and every African soldier had gonorrhoea at least once a year. Syphilis was very rarely diagnosed.

We did not see many patients with leprosy because the vast majority of our men had been enlisted a very short time ago.

I saw a few patients with bilharzial disease. There were one or two cases of *S. mansoni* infection and slightly more of the other type. It was not common amongst troops and we had to deal with no more than one case in hospital at a time. We treated bilharziasis with stibophen.

Major EVANS has brought back a mass of material on sickle-cell disease. I understand that he is preparing a paper on this subject.\*

Jaundice was quite definitely seen in Africans with amoebic infection of the liver. I would not like to say that it was the effect of the amoebic infection but the jaundice cleared up whilst the patient was having the usual treatment with emetine. I think the jaundice on the whole cleared up faster than ordinary infective hepatitis jaundice.

Amongst the population in the Gambia there were quite extensive outbreaks of alastrim going on with deaths among children. The cases described looked far more like severe chickenpox, though one or two of them might have been some other condition and not chickenpox.

I was interested to hear of the high incidence of enlarged spleens recently found in West Africans in the Gambia. I had occasion, as a part-time hobby to examine civilians of the local population and a very large proportion of the children had definite splenic enlargement. I found 50 per cent. of the children had grossly enlarged spleens and about 20 per cent. amongst adults.

We also had a certain number of cases of worm infection which were often taken for cases of amoebic dysentery and in which the pathologist failed to find any amoebae or cysts. Guinea worm was frequently seen and was treated by the surgeons.

\* EVANS, R. WINTON (1944) Sickling phenomenon in the blood of West African natives. *Trans. R. Soc. trop. Med. Hyg.* 37, 4 281

No cases of enteric fever were seen in Europeans or Africans. In the cases of murine typhus the rising titre of *B. proteus* OX 19 occurred late in some cases as late as the 21st and up to the 30th day. The rise of titre varied from 1:200 to 1:1000.

We had many cases of infective hepatitis in Europeans within 3 months of yellow fever inoculation. This followed inoculation with two batches used in this country (October 1942, and again December 1942).

## COMMUNICATIONS

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### PIGMENT METABOLISM AND RENAL FAILURE IN ACUTE SULPHONAMIDE HAEMOLYSIS RESEMBLING BLACKWATER FEVER.

BY

HENRY FOY\*

JOHN GLUCKMAN MAJOR

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AND

ATHENA KONDI

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#### INTRODUCTION

The various intravascular haemolyses will broadly resemble one another in their blood pigment metabolism and other blood changes. This has in fact, been found to be the case in such conditions as blackwater fever incompatible transfusions haemolytic jaundice and haemolysis from various drugs. The extent and duration of the haemolytic process will obviously affect the amount and types of pigments found as well as the other blood changes.

Numerous reports have appeared during the past few years describing acute haemolysis following the exhibition of different sulphonamides. Some of these reports have dealt with cases in which it was impossible to say whether there was actually any intravascular haemolysis or not, the authors merely describing dark urine, no blood counts or spectroscopic examinations of the plasma or urine having been made. In other cases it seems that haematuria is being confused with haemoglobinuria. Disregarding these uncertain cases there are, however a number of undoubted examples of acute massive haemolysis accompanied by haemoglobinaemia and haemoglobinuria following the administration of sulphonamides and accompanied by profound falls in the red cell counts. (HARVEY and JANEWAY 1937 KOHN 1937 WOOD 1938 STRASSER and SINGER 1939 KEEFER 1939 TAVAT and SHEPARD 1939 GILLIGAN and KAPNICK 1941 QUICK and LORD 1941

\* Our thanks are due to the DIRECTOR GENERAL OF MEDICAL SERVICES (S.A.) for permission to publish this case, and to Dr JOSEPH GILLIGAN of the Witwatersrand University for the histological examination and report.

In the case outlined below complete quantitative pigment estimations in blood and urine were made, and correlated with other blood findings, so that a comparison between the pigment metabolism in this condition, blackwater fever and the other intravascular haemolyses was possible, bringing out the resemblances and differences between them.

As will be seen from the findings there was a typical acute intravascular haemolysis, accompanied by methaemalbuminaemia, haemobilirubinaemia, and intracorpuseular methaemoglobinæmia and fall in the red cell count. Terminally the patient became anuric and azotemic, died, and a postmortem was done.

#### CASE REPORT AND POSTMORTEM FINDINGS

On 16th February 1943 a European male was admitted to hospital suffering from an eczematous dermatitis of the arm, which, after admission, developed into a cellulitis. He was given 15 grammes of benzyl-sulphanilamide (M & B 123) over a period of 3 days.

18th February.—After receiving 12 grammes a slight serous tint of his conjunctivæ was noted.

19th February.—A further 3 grammes were given after which the patient passed a quantity of dark coloured urine.

20th February.—The sulphanilamide was discontinued as the patient became extremely ill, deeply jaundiced and complained of pain and exhibited tenderness in both loins and in the gall-bladder region. His liver was felt about half an inch below the costal margin. At 11 a.m. he passed 180 c.c. of mahogany-coloured urine containing 55 mg. per cent of oxyhaemoglobin with a pH of 5.3 (electrometric). The deposit revealed brown granular casts and amorphous debris and there was a considerable amount of albumin. He subsequently passed 210 c.c. of urine at 3 p.m. containing 108 mg. per cent of oxyhaemoglobin and 835 mg. per cent of methaemoglobin. At 11 p.m. a further 40 c.c. was passed containing 275 mg. per cent of oxyhaemoglobin and 470 mg. per cent of methaemoglobin. The pH remained at 5.3. His blood pressure was 120/90, erythrocytes 1.8 million per cu. mm., leucocytes 50,000 per cu. mm.

Careful cross-examination both of the patient and his wife excluded any history of malaria, or malaria-like illness or any dosage of prophylactic quinine and slides examined at that time and repeatedly throughout his illness revealed no evidence of malaria parasites. In addition, there was no history of previous administration of any of the sulphonamide drugs. His past history had nothing of any significance.

The temperature fluctuated around 101° F. with a pulse rate of 100. The diagnosis of acute intravascular haemolysis associated with the administration of sulphanilamide was made and treatment and investigation instituted on that basis.

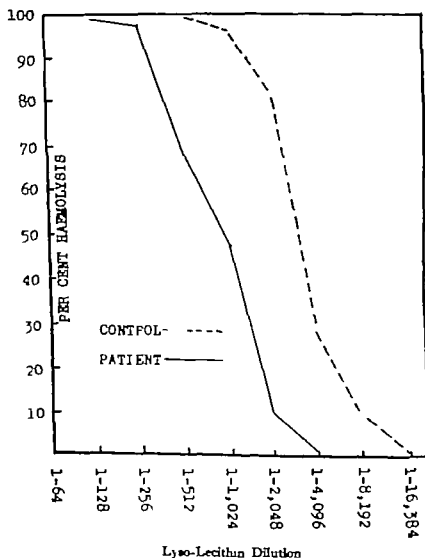
Intravenous glucose saline was commenced, and an hour later 500 c.c. of Group "O" blood were given. The patient's group was "O" and direct compatibility tests were performed before and after transfusion. After 300 c.c. had been administered the patient had a very severe rigor but complained of no pain or acniation in the chest or lumbar region. The temperature rose to 104° F. and the transfusion was stopped. He recovered from this crisis within a few hours.

21st February.—The patient was drowsy, total urinary output for the day was 60 c.c. containing both oxyhaemoglobin and methaemoglobin (see Table I p. 308). Diathermy was given to both kidneys for 10 minutes with no results. A continuous intravenous glucose saline was running to which had been added 10 grammes of sodium bicarbonate. The effect of this single administration of alkali as will be seen in the table was to lift the pH of the urine from 5.0 to 7.8 (electrometric). B.P. was 120/70. A 500 c.c. blood transfusion was given through a Y-tube together with saline with no untoward consequences. Blood urea, 193 mg. per cent. By 4 p.m. B.P. 190/100, temperature 99° to 100° F. pulse racing. At 6 p.m. a further 500 c.c. blood transfusion was started. B.P. 150/70, blood urea, 278 mg. per cent.

Throughout this period he took fluids freely by mouth (Table I) but had waves of nausea and he vomited small quantities of bile stained fluid. Excessive perspiration was a marked feature of his condition. Details of fluid intake and output are shown in Table I.

*22nd February*—After a good night he passed at 6 a.m. 8 c.c. of much lighter urine containing only traces of oxyhaemoglobin. B.P. at 8.30 a.m. 160/85 500 c.c. of blood given and at 11 a.m. he passed 10 c.c. of perfectly clear urine. Erythrocytes 2.09 million per cu. mm. leucocytes 32 000 per cu. mm. and blood urea, 263 mg per cent.

GRAPH 1—LYSO-LECITHIN FRAGILITY



The plasma contained 291 mg per cent. of methaemalbumin (623 m $\mu$ ) and 90 mg per cent. of oxyhaemoglobin (Hartbridge reversion spectroscopy).

*23rd February*—Passed 45 c.c. of clear urine, was stuporous with bouts of excitement, there was a deterioration in his condition. B.P. was 160/55 blood urea 371 mg per cent. A complete blood examination done on this day is given in Table II and for the other days in Table V.

The fragility of the red cells to saline and lyso-lecithin was as indicated in Tables III and IV and Graphs 1 and 2 and Price-Jones curve in Graph 3. The Kahn test and blood culture were both negative.

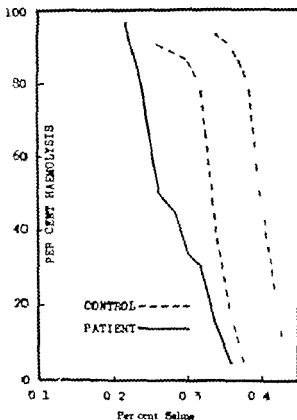


24th February.—Little change blood urea 358 mg per cent. B.P. 175/55 erythrocytes, 3.4 million per cu. mm. and leucocytes 20 000. Rales were heard at the right base and a small patch of consolidation. Passed 45 c.c. of clear urine.

25th February.—The jaundice was diminished and the man rational. Blood urea, 468 mg per cent. Urinary output for the day was 25 c.c.

26th February.—The improvement seemed maintained and he passed a little more urine. Blood urea was 512 mg per cent. and the B.P. 140/100. Later in the evening however the patient gradually collapsed and died.

GRAPH 2.—SALINE FRAGILITY



#### POSTMORTEM REPORT

Autopsy was performed 5 hours after death, permission having been granted for the thorax and abdomen only.

**Thorax.**—There was no fluid in either pleura. Both lungs showed sub-pleural petechiae and the base of the right lung was oedematous. The heart and pericardium appeared normal.

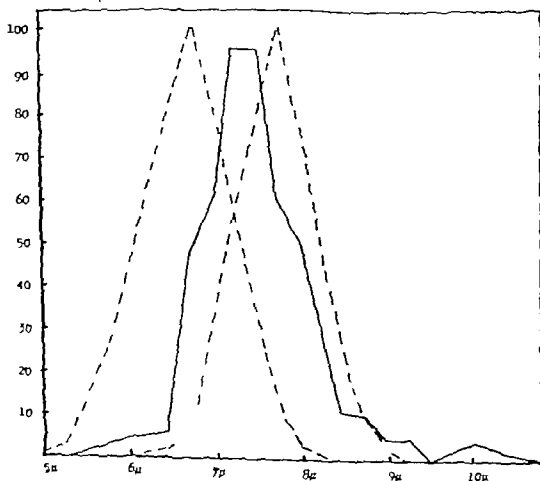
**Abdomen.**—Liver was enlarged and hard. The gall-bladder wall was

oedematous and fully half an inch in thickness. The bladder was full of cheesy black bile but there was no obstruction in any part of the duct system.

The pancreas was hard and the consistency was "woody"

The kidneys did not appear grossly enlarged and the capsule stripped easily. On section they were a deep purple in colour extremely congested and oedematous and it was barely possible to distinguish cortex from medulla. The renal pelvis ureters and bladder were all empty, patent and of normal appearance.

GRAPH 3 -- PRICE JONES CURVES



The suprarenal glands were small and atrophic. The spleen was slightly enlarged congested, hard and of a deep purple colour. Except for a small encapsulated abscess in the left tonsil all else was normal. Tissue was removed from all organs for histological examination.

Detailed histological study of this case will form the subject of a separate report elsewhere but a brief description of kidney, liver and gall bladder is of interest.

TABLE I  
 URINE OUTPUT AND FLUID EXCHANGE

Date	Time Passed	Amount Passed	Oxyflb Mg	Metflb Mg %	pH Electro- metric	24 hours Urea Mg	Deposit	Parenteral Serum Glucose c	Oral Fluids c	24 h Urine Output c	Transfusions	
											Amount c	Time
20.2.43	11 m	180	58	N/	8.2	—	Granular casts Amp N R B C Ren- al Cells Albumin ++	800	1 250	410	700	3 p m
	3 p m	210	108	85%	5.3	—						
	11 p m	40	77.5	670	5.3	—						
24 hrs												
21.2.43	5 m	30	185	N/	4.9	—		1 200	1 250	60	500	12.13 p m
	8.30 p m	20	220	256	5.0	—		+			500	5 p m
	9 p m	10	230	N/	7.0	—		(10 granules and bacilli)				
24 hrs												
22.2.43	8 a m	8	10	N/	7.8	4.90 mg %	clear	800	1 250	18	300	8 a m.
	11 m	10	clear	clear	6	—						
	3.30 p m	18	10	—	—	—						
24 hrs												
24.2.43	8 m	15	clear	clear	—	1 370 mg		—	1 400	45	—	—
	11 a m	18	—	—	—	—						
	3.30 p m	18	—	—	—	—						
24 hrs												
24.2.43	3 m	45	—	—	—	—		1 000	1 500	45	—	—
	6 m	18	clear	clear	—	200 mg %						
	11.30 a m	15	—	—	—	—						
24 hrs												
25.2.43	4 m	45	—	—	—	—		—	1 500	25	500	9 p m.
	8 m	15	clear	clear	—	—						800 c c.
	11 m	10	—	—	—	—						(withdrawn at above time)
24 hrs												
26.2.43	Morning	18	clear	clear	—	—		800	600	42	—	—
	Afternoon	12	—	—	—	—						
	Evening	18	—	—	—	—						
24 hrs												
26 hrs		45	—	—	—	—						
		—	—	—	—	—						
		—	—	—	—	—						

TABLE II  
BLOOD FINDINGS February 23rd

Erythrocytes	2.05 million per cu. mm.
Haemoglobin	7.5 grammes (Newcomer)
Colour Index	1.2
Leucocytes	23 000 per cu. mm.
Haematocrit	22 per cent.
Reticulocytes	10 per cent.
M.C.V.	110 $\mu^3$
van den Bergh	10 mg. per cent. (indirect)
Schumm's Test	Positive ++ (a band at 558 m $\mu$ .)
Methaemalbumin	97 mg per cent. (623 m $\mu$ )
Oxyhaemoglobin	Nil
M.C.D. (Price-Jones)	7.53 $\mu$ $\sigma = 0.89$ V 9.0 per cent
M.C.T.	2.4 $\mu$
Volume Index	0.91
Corrected M.C.V.	81.9 $\mu^3$
Diameter/Thickness ratio	3.1.1
Volume/Thickness index	1.34
Surface area ( $0.64 \pi D^2$ )	114 $\mu^2$

TABLE III  
SALINE FRAGILITY

Per cent. Saline.	Per cent. Haemolysis		Per cent. Saline	Per cent. Haemolysis.	
	Control.	Sulphonamide.		Control.	Sulphonamide
0.22	100	100	0.36	95	5
0.4	100	80	0.38	80	—
0.6	100	50	0.40	50	—
0.28	100	45	0.42	20	—
0.30	100	35	0.44	5	—
0.32	100	20	0.46	—	—
0.34	98	15	0.48	—	—

TABLE IV  
LYSO-LECITHIN FRAGILITY

Lyso-Lecithin Dilution	Haemolysis Per cent.		Lyso-Lecithin Dilution.	Haemolysis Per cent.	
	Control.	Sulphonamide.		Control.	Sulphonamide.
1 in 1.3 L.L.	100	100	1 in 2,048 L.L.	81	10
1 in 256 L.L.	100	99	1 in 4,096 L.L.	29	0
1 in 512 L.L.	100	68	1 in 8,192 L.L.	—	—
1 in 1,024 L.L.	98	48			

In the kidney the outstanding feature was the wide separation of the tubules by intensely oedematous tissue, in which the reticular fibres were unusually obvious. Lying in the oedematous mass were pools of coagulated lymph and focal aggregation of plasma cells, especially marked in the region of the large calyces. The oedema nowhere tended to compress the tubule. In the proximal convoluted tubules the epithelium was degenerated, and the nuclei irregular and of bizarre shapes. In many areas desquamated cells from the convoluted tubules were seen to be lying free in dilated tubules, surrounded by eosinophilic debris. In such tubules the basement membrane was thick and opaque.

The majority of the glomerular tufts with their epithelium, and capsular spaces appeared normal.

There was a great difference in the appearance of the kidney in the paraffin and frozen material. In the former as stated above, the tufts and capsular spaces appeared to be normal. In the frozen material on the other hand, where the distortion due to dehydration is absent the glomerular tufts almost completely filled the capsule, and the spaces were consequently very much reduced in size. The tubular epithelium in the frozen sections showed much less separation from their basement membranes and the granular debris almost filled the lumen with loose masses which by no means blocked the tubules. It seems to us that in investigating the histological changes that take place in these anuric conditions the frozen material is a better guide to what is taking place than are paraffin sections.

The distortion due to dehydration, as will be seen from Plate Figs. 1 and 2, produces a very misleading picture of the changes going on in the various kidney elements.

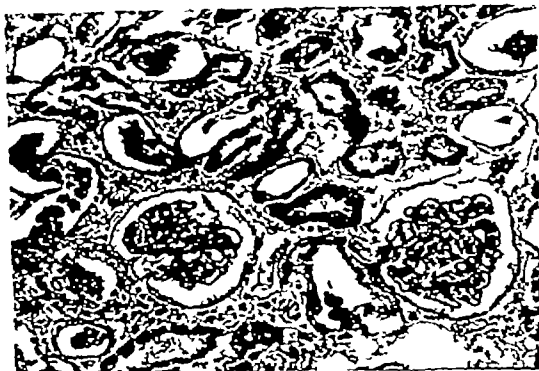
The dominant feature about the liver was the total absence of pigment from the Kupffer cells, and it is difficult to conceive that this could be due to the rapid formation of bilirubin. Some failure of the reticulo-endothelial system may have been responsible.

In addition the central vein was distended, and the hepatic cells in the related trabeculae were atrophic. The reticulum was pronounced and appeared to be separated from the liver cells. The gall-bladder showed no catarrhal changes or desquamation of the epithelium. Goblet cells were seen in great profusion. Oedema of all layers was intense and there were many histiocytes loaded with pigment.

## DISCUSSION

In deciding whether a case is haematuria or haemoglobinuria, spectroscopic examination of the plasma and urine for the detection of haemoglobin or its derivatives is essential. The existence of red blood cells in the urine will at once cast doubt on a diagnosis of haemoglobinuria. In examining urine for haemoglobin the fluid should be freshly passed so as to reduce the chances

FIG 1



Kidney Section  $\times 200$  (Paraffin material)

FIG 2.



Kidney Section  $\times 200$  (Frozen material)



of destruction of any red cells and thus give rise to a false diagnosis of haemoglobinuria. The presence of methaemoglobin in the urine should immediately lead to the suspicion of true haemoglobinuria. A haemolysis that is sufficient to produce a haemoglobinuria will show a haemoglobinaemia if the blood is taken during or immediately before the access of haemoglobinuria. The presence of a haemoglobinaemia is the final court of appeal in deciding whether we are dealing with haemoglobinuria or haematuria. In addition to the presence of oxyhaemoglobin in the plasma other pigments indicative of an intravascular haemolysis will generally be found, such as haemobilirubin and methaemalbumin. In addition, Schumm's test will be positive and this is regarded (FAIRLEY 1941) as indicative of amounts of methaemalbumin which are too small to be detectable by spectroscopic examination, even in great stratum thicknesses. All these haemoglobin derivatives have been found in conditions where intravascular haemolysis has occurred, such as blackwater fever haemolytic jaundice, incompatible transfusions and poisoning by various drugs.

In the case reported here all three pigments were present, as well as intracorpuseular methaemoglobin, thus establishing that the haemoglobinuria was due to a pre-existing intravascular haemolysis. The pigment estimations were carried out by means of a Hartridge reversion spectroscope.

There is a certain amount of confusion concerning the types of pigments present in the haemolyses that sometimes accompany the administration of sulphonamides. Some authors have stated that they find neither methaemoglobin nor sulphaemoglobin even though large amounts of sulphonamides have been given (CARNAVA, 1940). MARSHALL and WALZL (1937) pointed out that since the oxygen carrying capacity of the blood in such drug toxicities is low when compared with its iron content, there must be some non-functional iron containing pigment present in the blood and they suggested methaemoglobinaemia, and later identified this pigment but did not rule out the possibility of sulphaemoglobin also being present.

The recent spectrophotometric, and spectrographic work of HARRIS and MICHEL (1939) and Fox and OTTENBERG (1941) and Fox and CLINE (1940) has settled the question of pigment metabolism in these sulphonamide toxicities. The findings of these workers has established that intracorpuseular methaemoglobin, plasma methaemalbumin oxyhaemoglobin and haemobilirubin are all present, and that the urine may contain either or both oxyhaemoglobin and methaemoglobin. A much rarer pigment is sulphaemoglobin. No sulphaemoglobin was found in the present case.

It is recognized that a greater or lesser degree of methaemoglobinaemia is consequent upon sulphonamide administration. There appears to be no relation, however between the occurrence of methaemoglobinaemia and sulphaemoglobinaemia. The latter is not positively correlated with blood sulphonamide levels but is dependent on a third factor *viz.*, sulphides hence desirability of restricting sulphur-containing foods during sulphonamide therapy. NIBLOCK



(1941) has, however, pointed out that diets containing sulphur have probably no relation to the development of sulphhaemoglobinaemia. Methaemalbumin aemia is dependent upon the extent and duration of the haemolytic process, and if this is small and of short duration the haemoglobin liberated will be dealt with by the intracorpuseular disposal mechanism, and haemobilirubin will increase. If on the other hand, the haemolysis has been large and acute, or long continued then the extracorpuseular disposal mechanism will come into play and the free haemoglobin in the plasma will be broken down to haematin and will then combine with plasma cystalbumin to form methaemalbumin. (FAIRLEY 1941)

A point of considerable interest is the presence of intracorpuseular methaemoglobin in the sulphonamide haemolyses and its absence so far as is known in blackwater fever in the other intravascular haemolyses nothing is known concerning its presence or absence.

Methaemoglobin is an oxidation product of haemoglobin, the iron moiety being converted from the divalent to the trivalent state. Such conversions can be accomplished by means of a number of oxidising agents, such as potassium perchlorate which will perform this oxidation both *in vivo* and *in vitro*.

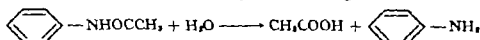
There are, however, a number of substances such as aniline, acetanilide, plasmoquine, nitrobenzene, as well as sulphonamides that are not oxidising agents *per se* but which do produce methaemoglobinaemia (HEURNER 1913 HEURNER *et al* 1923 Foy and KONDI, 1938). In the case of aniline and acetanilide the production of *p*-aminophenol and its derivatives, such as quinoneimine, have been shown to be responsible for methaemoglobin production (HEURNER & SCHWEDTKE, 1936 BERNHEIM, 1942).

Whether the production of *p*-aminophenol is responsible for the methaemoglobinaemia in the case of sulphonamides is uncertain. RIMINGTON (1939) has suggested that it may be and that semiquinones may play a part in the oxidation of haemoglobin to methaemoglobin. JAMES (1940) states that *p*-aminophenol occurs in the urine of animals given sulphonamides. It has, however, been pointed out by THORPE and his co-workers (1941) that the tests used for the identification of *p*-aminophenol were not specific, and on theoretical grounds it seems unlikely that the  $\text{NH}_2\text{SO}_2$  group could be removed from the sulphanilamide ring *in vivo* and allow the formation of the end products that are reputed to be responsible for the production of methaemoglobin.

Methaemoglobincythaemia is of less serious consequence than sulphhaemoglobincythaemia since the former reverts to oxyhaemoglobin in a few days and its disposal can be hastened by means of methylene blue administration. It is not known whether the acceleration of methaemoglobin disappearance by means of methylene blue is due to direct reduction of the methaemoglobin by methylene blue, or to the fact that the substance responsible for the oxidation of haemoglobin to methaemoglobin reacts with methylene blue instead of with haemoglobin. Irrespective of what mechanism is involved, it should be possible,

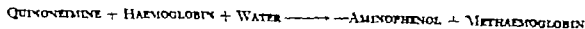
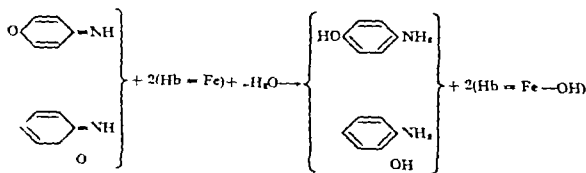
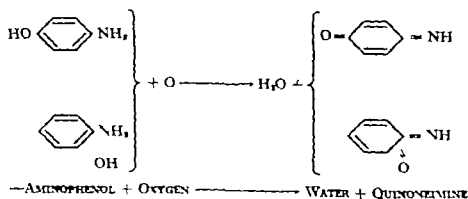
theoretically for any substance capable of facile reversible oxidation and reduction to bring about the same result as does methylene blue. A very suitable substance from this point of view would be ascorbic acid on account of its high reactivity and non toxicity. In this connection it should be mentioned that glutathione which is present in high concentration in red blood cells (MORRISON and WILLIAMS 1938) may be one of the mechanisms that is responsible for preventing the accumulation of methaemoglobin *in vivo* the known ability with which certain of the sulphonamides penetrate the red cells may upset the normal glutathione-methaemoglobin preventing mechanism, and permit the appearance of intracorpuseular methaemoglobin. In a future paper we are dealing with the question of methaemoglobin formation in certain of the intravascular haemolyses and further discussion of this will be left until then

The reaction can be represented by the following scheme —



ANILINE

— AMINOPHENOL



Date 1943 F b	R.B.C. Millions per c.c.m.	Hb. % Sahl	W.B.C	Reticulocytes	Haematocrit %	M.C.V $\mu^3$
"0	1.8 (1 m)	4	4900	—	20	111
1	3 (11 a.m.)	60	50,000	—	—	—
—	6.9 (8.30 a.m.)	75	3,000	—	31	109
"2	2.0 (10.30 m)	54 7.5 gm	33,000	1 10	— 22	110
4	2.4 (1 m.d.d.a.)	—	31,000	—	—	—
5	5 (11 m)	49	33,000	—	—	—
"6	(1 m.d.d.a.)	53	2,000	10	—	—

Very little is known concerning the means by which methaemoglobin makes its appearance in the urine—that it is not related to plasma methaemalbumin, or intracorpuseular methaemoglobin seems fairly clear or that pH changes and ionic concentration of the urine are not the only or most important factors at work.\* In crush injuries myohaemoglobin has been reported in the urine. In addition to the haemolysis in these sulphonamide toxicities there occurs in some cases a great reduction in the output of urine, similar to that which is often present in blackwater fever and the other intravascular haemolyses, and which may pass into complete anuria. The majority of such cases of anuria that occur in the sulphonamide toxicities have been shown to be due to mechanical blockage of the upper parts of the urinary tract with crystalline derivatives of the drug, which may lead to traumatic haematuria and anuria. There are, however, on record a number of cases where such mechanical blockage and injury can be ruled out and in which the explanation of the anuria must be sought elsewhere.

We have dealt in an earlier paper (FOY, ALTMANN, BARNES and KONDI 1943) with the renal failure that occurs in such haemolytic conditions as blackwater fever, incompatible transfusions and sulphonamide toxicity and with that which occurs in crush injuries. Similar renal findings have recently been

RUBEL (1938 and 1939) has shown that urochrome and certain other urinary pigments will convert haemoglobin into methaemoglobin *in vitro* in the absence of oxygen.

V

## FINDINGS.

Sedimentation 1 hour	Blood Urea Mg %	Plasma or Serum Pigments.			Fragility
		OxyHb.	MetHb	MetAlb.	
74 mm.	—	+++	Nil	+	0.34-0.22
—	193 (11 a.m.) 278 (5 p.m.)	+++	Nil	+	—
68 mm.	263	90 mg %	Intra- corpuscular	29.1 mg %	0.28-0.28 Incomplete
—	371	Nil	Nil	97.5 mg %	—
—	358	Nil	Nil	Nil	0.26-0.22
—	468 (11 a.m.) 494 (8 p.m.)	Nil	Nil	Nil	—
—	512	Nil	Nil	Nil	0.24-0.28 Incomplete

described by YOUNG (1942) in utero-placental damage and by McLEITCH (1943) in severe vomiting.

In the case reported above there were changes in both the tubules and the glomeruli although abnormality of the latter was only visible in the frozen sections, a point worth further investigation since most authors have described no glomerular changes in the material dehydrated by fixatives.

The fluid intake and urinary output in the present case is shown in Table I together with data regarding the blood transfusions and urine analyses. As will be seen there was a steadily diminishing flow of urine, in spite of an adequate fluid intake. There appeared to be no relation between the urinary flow and variations in systemic blood pressure as will be seen from Table VI.

TABLE VI  
BLOOD PRESSURES.

Date	S/D	Time	Date	S/D	Time
20	120/70	—	21	160/65	—
21	120/70	10 a.m.	22	160/55	8.30 a.m.
21	190/100	3 p.m.	24	190/85	8.30 a.m.
21	150/70	5 p.m.	24	175/55	2 p.m.
21	140/70	8 p.m.	25	175/80	8.30 a.m.
22	160/65	8.30 a.m.	26	140/100	8.30 a.m.
22	160/65	—			

It appears that the renal failure that occurs in all these conditions has a similar basis, and cannot be explained as a result of the operation of any single factor such as blockage of the lumina of the renal tubules with products of haemoglobin precipitated from an acid urine (BAKER and DODDS 1925). Recent work seems to indicate that a great many factors may be involved in the renal failure in these conditions, among which may be mentioned diminished glomerular filtration due to a variety of causes, such as dehydration, actual or physiological, disturbances in acid base-electrolyte-water balance and upsets in the permeability of the glomerular membrane, etc.

Reduction in blood flow might especially affect the tubules on account of their high oxygen requirements and lead to degenerative changes followed by upsets in tubular reabsorption and concentration. These changes in glomerular filtration and tubular reabsorption and their concomitant sequelae would lead to piling up of necrosed matter and haemoglobiniferous material in the tubules, and thus any blockage would be the result of antecedent factors, and not itself the cause of the anuria or azotemia (FOY *et al.*, 1943).

BRADFORD and SHAFER (1942) and GROES, COOPER and MORNINGSTAR (1942) have described the appearance of the kidneys in cases of death from sulphonamide haemolysis and anuria and have noted cloudy swellings, and degenerative changes in the tubular cells, as well as glomerular changes which they consider are the cause of the anuria.

We have no explanation for the severe reaction that occurred during the first transfusion. Since it occurred after only 300 c.c. had been given it might point to low titre Landsteiner group incompatibility. The large number of successful transfusions that have been given by this unit would seem to rule out pyrogens or insufficiently cleaned apparatus. ROTHSTEIN and COHEN have stated that iso- and pan-agglutination occurs in some cases after sulphonamides, but neither in this nor in his cases can the factors mentioned above be ruled out.

It should be borne in mind that such auto- and pan-agglutination is common in many severe anaemias as well as in liver diseases (WIENER, 1939) and it is not necessary to incriminate sulphonamides to account for these phenomena, in either this or ROTHSTEIN's case. Agglutination and spherocytosis are generally regarded as precursors of haemolysis, and according to HAIN and CASTLE (1940) are associated with changes in the osmotic fragility of the red cells to saline. As has been pointed out elsewhere (FOY and KONDI 1943) it is not always possible to associate changes in osmotic fragility with either *in vivo* haemolysis or spherocytosis so far as blackwater fever is concerned. That in some conditions changes in the diameter thickness ratio may be linked with variations in osmotic fragility is probably true, but it cannot be regarded as an invariable linkage. HAIN and CASTLE consider that in the haemolyses that occur in icterus gravis neonatorum, haemolytic jaundice, and after some drugs, circulating haemolysins are not the cause of the red cell destruction, but that there is some defect in the red cell itself that renders it more liable to haemolysis,

following stasis, agglutination and spherocytosis. That the changes considered by these workers are secondary to more fundamental ones occurring in the cells environment is shown by the fact that removal of the spleen in haemolytic jaundice stops the periodic haemolyses but leaves the fragility of the red cells unchanged. In blackwater fever normal red cells transfused into a haemolysing case are broken up just as are the patients' own cells (FOY and KONDI 1941) and in icterus gravis neonatorum Rh factors are probably behind the haemolysis. That the situation is however by no means a simple one is brought out by the recent work of CRUZ and his colleagues (1941) who have shown that red cells 'labelled' with radio-active isotopes of iron are more likely to be destroyed if young than if they are more mature.

ANTOPOL *et al* (1941) state that in rats given sulphonamides there is an increase in the resistance of the red cells to saline, whether the increase seen in our case is due to the same cause is impossible to say, in COOLEY'S anaemia the same phenomenon is present (WINTROBE, 1942).

The greatly increased resistance to both saline and lyso-lecithin noted in the present case was not associated with any abnormality in the Price Jones curves and the mean cell diameters, volumes, thicknesses and ratios were all within normal range, as will be seen from the charts.

The volume thickness index and diameter thickness ratio appear to be intermediate between normal and blackwater fever if HADEN'S figures for normal values are taken. As, however, HADEN gives only absolute values, and not normal ranges comparisons are not of much value. The figures in the present case are very different from those obtained in haemolytic jaundice (FOY and KONDI 1943).

The surface areas calculated from Knoll's formula ( $0.64 \times \pi D^2$ ) are normal.

### SUMMARY

1. Attention is directed to the resemblances and differences in blood pigment metabolism in such conditions as blackwater fever, haemolytic jaundice, and the intravascular haemolysis that sometimes occurs after sulphonamides. It is noted that intracorpuseular methaemoglobin occurs after sulphonamides, plasmoquine and acetanilide but does not occur in blackwater fever so far as is known. Oxyhaemoglobin, methaemalbumin and haemobilirubin are common to all of the intravascular haemolyses.

It appears that *p*-aminophenol or a derivative thereof is responsible for the methaemoglobinaemia that occurs after aniline and acetanilide, whether or not similar metabolites are responsible in the case of sulphonamides and plasmoquine seems uncertain.

2. In the present case there was an acute massive intravascular haemolysis accompanied by the presence of plasma oxyhaemoglobin, methaemalbumin and haemobilirubin as well as intracorpuseular methaemoglobin and a profound fall in the red cell count.



## TECHNIQUE AND INTERPRETATION OF THE WEIL-FELIX TEST IN TYPHUS FEVER\*

BY

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The following notes have been prepared in response to requests for a brief account of the technique and interpretation of the Weil Felix reaction. Much of the recent work on the typhus group of fevers has been published in English but the extensive earlier work on the Weil-Felix reaction in classical louse borne typhus appeared in foreign literature and is known to the younger generation of clinicians and pathologists in this country merely from the scanty references given in the textbooks. Even the article on typhus fever in *A System of Bacteriology* (FELIX, 1930) does not contain adequate information on the clinical and epidemiological aspects of the test.

The three serological varieties of *Proteus*  $\lambda$ , known as OX19 OX2 and OXK are no longer the only reagents by means of which the serological diagnosis of the different varieties of typhus can be made. Suspensions of rickettsiae can now be obtained in relatively large quantities by growing these organisms in the yolk sac of the developing chick (Cox, 1938) or in the lungs of infected rats and mice (CASTANEDA 1939). Purified rickettsial suspensions are now being tried in agglutination and complement fixation tests with typhus sera in various parts of the world and there can be little doubt that this work will lead to important advances in the serology of the typhus group.

Rickettsiae possess heat labile and heat stable antigens (CASTANEDA and ZIA, 1933) and sera from typhus patients contain, or may contain the corresponding two kinds of antibody. In the future an improved method of serum

\* A report to the Medical Research Council.



diagnosis of the typhus fevers is, therefore, likely to be based on the separate estimation of the two different rickettsial antibodies, much in the same way as the enteric fevers are now diagnosed by the demonstration of H and O agglutinins for each of the members of the typhoid paratyphoid group. Even a third type of reagent is required in the so-called Vi agglutination test for the detection of chronic typhoid and paratyphoid carriers. So far three specific O antigens of typhus rickettsiae have been identified which these organisms share with the three serological varieties of *Proteus* V. The three O antigens are available in the most convenient form in suspensions of *Proteus* O\19 O\2 and O\K. What is needed are suitably prepared reagents for the estimation of the antibodies to the heat-labile rickettsial antigens. It was mentioned in a previous paper (FELIX, 1942) that the heat labile and heat-stable antigens of *Rickettsia prowazekii* behave similarly to the Vi and O antigens of *Bact. typhosum*. The heat labile antigen of rickettsiae inhibits the interaction between the heat stable antigen and its corresponding antibody in the same manner as the Vi antigen does in the case of the O antigen of the typhoid bacillus. The results so far obtained with rickettsial agglutination tests are rather confusing. Some workers have reported almost complete parallelism between agglutination of *R. prowazekii* and *Proteus* O\19 whereas others obtained quite different results. This seems to indicate that some of the rickettsial suspensions, as at present prepared, are not entirely insensitive to the O antibody and do not, therefore, serve as pure reagents for the antibody to the heat labile rickettsial antigen. Nevertheless, it has already become possible by means of complement fixation and agglutination tests with rickettsial suspensions to distinguish between some of the varieties of the disease which give overlapping reactions to the *Proteus* O\ antigens (BENGTSON and TOPPING, 1942; PLOTZ, 1943; VAN ROOYEN and BEARCROFT 1943; STEART HARRIS, RITTIE and OLIVER, 1943). The relative usefulness of diagnostic tests with suspensions of rickettsiae and *Proteus* O\ strains in the early diagnosis of cases and in the retrospective diagnosis of missed ambulatory patients is a problem which remains to be investigated.

For the present, however, most pathologists must continue to rely on the agglutination test with *Proteus* O\ antigens as the sole test available for the routine diagnosis of cases of typhus fever and for carrying out epidemiological surveys in localities where the disease is prevalent. The technique and interpretation of the test and its application by the clinician and epidemiologist are discussed in this paper mainly in relation to the louse-borne typhus of type O\19 the variety of the disease that is most dreaded. Louse borne typhus is usually referred to as epidemic typhus but it should be borne in mind that the disease is endemic in many parts of the world and gives rise to widespread epidemics only under conditions that favour louse-infestation. The term "louse-borne typhus," used throughout this paper applies to both the epidemic and the endemic form of the disease. The other typhus-like fevers are dealt

with in less detail and only those varieties are discussed here which occur in the countries that are at present, or soon may become a theatre of operations. Table I shows the fevers of the typhus group subdivided into three serological sub-groups according to the agglutination reactions obtained with the three different *Proteus* OX antigens.

TABLE I.

PROVISIONAL CLASSIFICATION OF THE TYPHUS GROUP OF FEVERS.

	Immunological Sub-group		
	Type OX19	Type OXk	Type Undetermined
Name of disease	Classical epidemic typhus Tabardillo (Mexico) Brill's disease (U.S.A.) Endemic typhus of U.S.A. and Australia Greece Syria Manchuria Malaya (shop typhus) India Burma Philip- pines, Hawaii Tonkin (fièvre nautique) etc.	Tsutsugamushi fever of Japan, Formosa, Malaya, and Dutch East Indies Scrub typhus of Malaya, Dutch East Indies India French Indo China Australia	Spotted fever of Rocky Mountains Spotted fever of eastern U.S.A. São Paulo typhus Fièvre boutonneuse (Mediterranean) Fièvre exanthématique of Marseilles Febbre eruptiva (Italy) Tick bite fever of South Africa Epidemic and endemic typhus of South Africa Tick-borne typhus of India Kenya, etc.
Vector	Lice and rat fleas	Mites	Ticks lice and rat fleas
Reservoir of virus	Rats Man	Field mice and rats	Rodents. Dogs ? Ticks Man
Agglutination	OX19 +++ OX2 + OXk —	OX19 — OX2 — OXk +++	OX19 + OX2 + OXk +

## LOUSE BORNE TYPHUS TYPE OX19

## TWO DIFFERENT FORMS OF THE CURVE OF AGGLUTININ PRODUCTION

Soon after the introduction of the Weil Felix test in routine diagnosis it was observed that cases of louse borne typhus show two different types of the curve of agglutinin formation. One type is characterized by the early appearance of agglutinins, high maximum titres and the persistence of a raised +

for a long time after recovery. In the second type the agglutinins appear comparatively late in the disease, reach only low titres and disappear early during convalescence. A number of reaction curves are reproduced here from earlier papers (FELIX, 1916-1917), since the figures demonstrate better than words how great is the difference between the two types of antibody response.

The cases listed in Table II came from an outbreak in a labour camp which was under careful medical supervision and some of the patients had been admitted to hospital as contacts even before the onset of symptoms (e.g., case No. 12). Accurate case histories were therefore available and fairly complete curves of the development of  $\Lambda$ 19 agglutinins were obtained. The cases recorded in Table III belonged to a series of 310 typhus cases that had been investigated in Constantinople in 1916-17. The following conclusions were drawn from these observations:

(1) The majority of cases of louse-borne typhus, approximately 75 per cent. of cases, show a significant  $\Lambda$ 19 reaction on or before the 4th or 5th day of illness, and the maximum titres reached shortly before or after defervescence are very high (mostly over 1:2000).

(2) The remaining 25 per cent. of cases show a positive reaction about the 6th or 7th day, in exceptional cases later still, and the maximum titres reached are very low (usually below 1:500).

(3) The type of the curve of agglutinin formation is related to the clinical course of the disease. There is no hard and fast rule but the relationship may be expressed in the simplest way as follows:

(a) The cases of moderate severity generally respond with high titres.

(b) The most severe cases, including the cases that succumb to uncomplicated typhus infection, have very low titres.

(c) The mildest cases, including the abortive cases and "inapparent" infections, may have either very low or very high titres.

Other workers who had a considerable experience of typhus during the war of 1914-18 put the ratio between cases giving a high-titre and those giving a low-titre reaction approximately in the order of 2:1 (ZLOCIST, 1917; OETTINGER, 1918; WOLFF, 1922).

It is of course not possible to draw a clear-cut line of demarcation between the two groups of agglutinin response. Nature does not draw the sharp distinctions that are so desirable for our purposes, and thus border-line cases occur which have an intermediate type of curve. It is, however, clear from the few examples given in Tables II and III that the difference between the maximum titres attained in the two groups is so great that it is impracticable even to prepare a graph using the same scale for the two types of reaction curve. It is futile to attempt to construct a curve of "average titres" compiled from observations on a large number of cases belonging to the two groups. Such attempts have been made recently in this country and abroad, but they are bound to obscure rather than elucidate the true picture of the rise and fall

TABLE II

SHOWING AGGLUTININ CURVES IN CASES OF LOUZE-BORNE TYPHUS OBSERVED IN POLAND DURING 1916.  
(Abstracted from paper by A. FELIX, 1916, *Wien klin. Wochs.*, 29 872.)

Case No.	Clinical Data.		Serum Examined	Agglutination with		Positive X19 Reaction first observed on
				Proteus X19	Proteus X2	
1	Onset	April 28	May 1	500++	25-	4th day of illness (1st day of rash)
	Rash appeared	May 1	" 3	5,000++	25-	
			" 6	10,000++	25++	
			" 9	50,000++	50+	
	Temperature normal	" 11	" 12	20,000++	25++	
			" 19	5,000++	25-	
			" 27	5,000++	25-	
			June 6	1,000++	25-	
2	Onset	April 28	May 1	2,000+	50+	4th day of illness (1st day of rash)
	Rash appeared	May 1	" 3	5,000++	50+++	
	Temperature normal	" 6	" 6	7,500+	50+++	
			" 12	2,000+++	25+++	
			" 19	2,000+	25++	
	(Abortive case)		" 27	1,000++	25-	
			June 6	200++	25-	
4	Onset	May 2	May 4	50++	25-	3rd day of illness (Two days before rash)
	Rash appeared	" 6	" 5	50+++	25-	
			" 7	400++	25-	
			" 9	5,000+	50++	
	Temperature normal	" 15	" 12	10,000++	50+	
			" 19	50,000++	50+	
			" 27	2,000+++	25-	
			June 6	1,000++	25-	
10	Onset	May 28	May 30	25+++	25-	3rd day of illness (1st day of rash)
	Rash appeared	" 30	" 31	50++	25-	
			June 2	200++	25-	
			" 6	1,000+++	50++	
	Temperature normal	June 12	" 10	5,000+	100+	
12	Onset	June 1	May 31	25-	25-	4th day of illness (1st day of rash)
	Rash appeared	" 4	June 4	50++±	25-	
			" 6	500++	25-	
			" 8	7,500++	50++	
	Temperature normal	" 11	" 10	2,000++±	100+	
14	Onset	May 10	May 11	25-	25-	6th day of illness (2nd day of rash)
	Rash appeared	" 14	" 14	25-	25-	
			" 15	25++	25++	
			" 16	50++	25++	
			" 18	100++	25++±	
	Temperature normal	" 23	" 22	100++	50+	
			" 27	100+++	50++	
			June 6	50++	25+	
15	Onset	May 16	May 19	25-	25-	7th day of illness (3rd day of rash)
	Rash appeared	" 20	" 20	25-	25-	
			" 22	25+++	25++	
			" 23	50+++	25++	
	Died	" 25	" 25	500+++	50++	

TABLE III

SHOWING AGGLUTININ CURVES IN CASES OF LOCKE-BORNE TYPHUS OBSERVED IN TURKEY DURING THE WINTER 1918-1

(Abstracted from paper by A. FELIX, 1917 *Z. Immunitätsforsch.*, 28: 60.)

Case No.	Clinical Course	Day of Illness	Titre of Agglutination with		X19 Agglutinin Curve
			Proteus X19	Proteus N.	
65	Moderately severe	5	200	0	High-titre curve
		7	1,000	50	
		10	1,000	100	
		12	1,000	100	
		1	1,000	50	
643	Moderately severe	5	500	0	High-titre curve
		7	5,000	50	
		10	10,000	50	
		15	5,000	1	
		18	1,000	50	
		20	1,000	15	
694	Moderately severe	4	100	0	High-titre curve
		6	500	50	
		8	1,000	100	
		11	10,000	100	
		16	4,000	100	
535	Moderately severe	1	0	0	High-titre curve
			20	0	
		4	200	50	
		10	10,000	300	
		14	10,000	500	
811	Moderately severe	1	10,000	500	High-titre curve
		5	1,000	0	
		14	1,000	50	
		22	1,000	20	
		26	1,000	20	
40	Very severe	43	1,000	0	Low-titre curve
		11	25	0	
		13	10	0	
		21	50	0	
		26	5	0	
56	Very severe	29	0	0	Low-titre curve
		7	5	0	
		1	100	50	
		14	100	50	
		26	20	0	
841	Very mild	44	20	0	Low-titre curve
		7	25	5	
		15	50	50	
		1	5	15	
		20	5	5	
573	Very mild	8	50	0	Low-titre curve
		9	20	0	
		10	100	0	
		29	10	0	
		23	20	0	

Titre 0 indicates a negative result in dilution 1:25

of the agglutinin titre in both groups. In order to derive full advantage from the use of the diagnostic test it is clearly essential to pay due attention to the distinctive features of the two types of reaction curve.

#### NORMAL OX19 AGGLUTININS AND RESIDUAL AGGLUTININS DUE TO A PREVIOUS TYPHUS INFECTION

The sera of normal persons contain low titre agglutinins for the *Proteus* A strains, even in natives of countries which for generations have been free from typhus. These normal agglutinins are of the O type, as are also those for typhoid and paratyphoid bacilli. The incidence and titres of normal agglutinins for OX19 and OX2 are lower than those for the enteric group of organisms. In a series of 1837 control sera from normal persons and patients suffering from various febrile diseases 7 per cent. agglutinated the strain X19 in a dilution 1/25 and 1/2 per cent. in a dilution 1/50 (see WEIL 1920). These results were obtained during 1916-18 using live suspensions of the H + O variant of the strain X19 and the fractional titres should, therefore, be multiplied by 2 in order to indicate the figures for the O variant which is now in general use. When an O variant is used the degree of O agglutination seen at the 24-hour reading is, as a rule, twice that for the corresponding H + O variant. Most workers fix the limit for normal agglutination with OX19 at 1/100 others prefer to put it at 1/200.

In countries with endemic typhus, where there is the possibility of persistence in the serum of residual agglutinins due to a previous infection, absolute diagnostic significance cannot be claimed for titres even considerably higher. The length of time during which a relatively high OX19 titre persists after the attack depends on the height of the maximum titre that had been attained during the disease. It has been stated in the previous section that the majority of cases of louse borne typhus develop what has been called the high titre curve of agglutinins. In these cases a retrospective diagnosis can usually be made from the agglutination test during 3 or 4 months following the attack of typhus, and in some cases even after a much longer interval. On the other hand, those patients whose serum exhibits a low titre curve of agglutinins during the disease may show a negative result in the OX19 test almost immediately after recovery. The residual OX19 reactions are of great value as an aid in the search for missed ambulatory patients and cases of so-called inapparent infection but at the same time they constitute a possible source of error in diagnosis.

The suspicion arose that non-specific stimulation of agglutinins which is one of the fallacies in the serum diagnosis of the enteric fevers would interfere also with the application of the OX19 reaction. It is known that H agglutination tests are useless as a means of diagnosing enteric infection in inoculated persons because of the non specific "anamnestic" rise in the H titre that

may occur in the course of other febrile conditions. Great care was therefore taken to investigate the possibility of non-specific rises in the O\19 titre. Typhoid patients who gave no history of previous typhus infection but showed in their serum "normal" agglutinins for O\19 in titres of 1/50 or 1/100 were observed during periods of several weeks or months and no significant fluctuation in the O\19 titre could be noted. Similarly patients with a definite history of a previous attack of typhus, whose serum contained residual O\19 agglutinins in titres ranging from 1/100 to 1/200 showed in no instance any evidence of non specific re-stimulation of these agglutinins in the course of typhoid, pneumonia and other febrile diseases (FELIX, 1929). It is worth mentioning that in this respect the O agglutinins for the *Proteus* \ strains behave in exactly the same manner as do the O agglutinins for the typhoid paratyphoid group of organisms.

#### EFFECTS OF ANTI TYPHUS INOCULATION

Inoculation against louse borne typhus has been introduced during the present war in the fighting services and in civilian hospital staffs and sanitary personnel. From experiences with laboratory infections among typhus workers, and from observations under field conditions such as have been published from German sources, it would appear that inoculation with the available vaccines does not protect effectively against subsequent infection but greatly reduces the severity of the disease. It is known that the clinical diagnosis of typhus is often not altogether easy and the modified mild disease in the inoculated may be almost impossible to diagnose without the aid of laboratory methods. It is therefore important to consider what effect anti typhus inoculation has on the development of O\19 agglutinins during a subsequent attack of typhus or some other febrile disease.

Vaccines made from rickettsiae of the O\19 group stimulate the formation of O\19 agglutinins in inoculated subjects. The titres are relatively low but the incidence of these inoculation agglutinins is stated by some workers to be very high. For instance, 57 per cent. of positive reactions have been recorded with Weigl's louse-gut vaccine, 73 per cent. with Zinsser's tissue-culture vaccine (LIU and ZIA, 1940) and nearly 100 per cent. with mouse lung vaccine (DURAND and GIBOUD, 1940). In comparative tests carried out in this country (FELIX, 1942) it was found that the various vaccines employed differed widely in antigenic value. One vaccine gave rise to a significant O\19 antibody response in 50 per cent. of those inoculated. Other vaccine groups showed considerably lower figures and one of the vaccines failed to stimulate any response at all. Table IV shows the rise and fall of these inoculation agglutinins in a group of twenty six volunteers from whom three samples of blood were examined, one before and two after the inoculations. Thirteen persons in the group who did not show a significant rise in titre are not included in the table.

The vaccine employed in this trial may be regarded as one of the most potent types of rickettsial vaccine at present available. The table shows that the inoculation agglutinins for OX19 reached only low titres, representing a mere fraction of the maximum titres that are attained in the majority of cases of louse-borne typhus\*. Only two of the inoculated persons (Nos 2 and 9) had the same agglutinin levels when tested 2 weeks and again 8 weeks after the third dose all the others showed a definite drop in the titre during the

TABLE IV

SHOWING THE OX19 AGGLUTININ RESPONSE IN VOLUNTEERS INOCULATED WITH EPIDEMIC TYPHUS VACCINE. (YOLK SAC VACCINE. BATCH C)

Case No	Agglutination of <i>Proteus</i> OX19		
	Before Inoculation.	Two Weeks after Third Dose	Eight Weeks after Third Dose.
1	25—	50±	*5—
2	50±	200±	*00±
3	25—	100+	30±
4	25+	100±	50±
5	50±	100±	50+
6	25—	100+	30±
7	25±	50+++	25++
8	25—	50±	25±
9	25±	50+	50+
10	25+	50+	25±±
11	*5—	50+++	25±
12	25±	*00±	50±±
13	50+	100±±	50±±

*Proteus* OX19 suspension prepared at Standards Laboratory (M.R.C.) Oxford

Reading after 24 hr (2 hr incubation at 37°C. and thereafter at room temperature)

+++ = strongest degree of agglutination supernatant fluid completely clear

± = weakest degree of agglutination which could be estimated with the naked eye

period of observation. It is thus seen that the OX19 antibody response to anti-typhus inoculation is of a moderate degree similar to the O-antibody response following T.A.B. inoculation. In this respect the heat stable O antigens of typhus rickettsiae and of typhoid and paratyphoid bacilli obviously behave in the same manner and they differ profoundly from the heat-labile H antigens. To the latter high titre agglutinins develop after T.A.B. inoculation and do not disappear from the circulation for many months or even years.

So far hardly any observations have been recorded to indicate the behaviour of inoculation agglutinins for OX19 during subsequent febrile diseases of

\* PENFOLD (1944) obtained very similar results in a group of twenty-three public health workers who had been vaccinated with the same batch of vaccine.



fact that the end titres of high titre sera may be somewhat lower than those read after incubation at 50° C

### *Sources of Error*

One of the most important sources of error in the test is H agglutination with *Proteus* X strains, since this type of agglutination is of no significance in the diagnosis of typhus. H agglutinins due to an existing or a previous infection with *Proteus vulgaris* such as cystitis, otitis, empyema, and wound infections, are occasionally met with in the serum of healthy persons or of patients suffering from various diseases. This pitfall has been eliminated by the introduction of preserved suspensions which consist of alcohol treated bacteria and do not, or should not, contain H antigen demonstrable by the agglutination test. In two recent papers (DAMMIN and BILLINGS, 1942; SONNENSCHIEIN 1943) however O agglutinins of the three *Proteus* OX types are stated to occur as a result of infection with strains of *Proteus vulgaris* possessing minor antigens of these types. SONNENSCHIEIN found that sera of this kind also agglutinated *Rickettsia prowazekii* to titres similar to those for *Proteus* OX19.

Another source of error may be briefly mentioned. Fresh sera of typhus patients may show a marked inhibition of agglutination over a zone of lower dilutions, usually in dilutions 1:25 and 1:50. The first appearance of agglutinins at the beginning of the disease, and the low titre reactions that have been discussed before may be entirely disguised by this phenomenon. In such cases after heating the serum for half an hour at 45° C a significant reaction may be obtained (for references see FELIX, 1930).

When examining samples of serum taken on successive occasions from the same patient it is most useful to store the remaining portion of the serum in the ice-chest and re test it simultaneously with the subsequent specimen. This procedure is a safeguard against possible variations in the agglutinability of different batches of the preserved suspension. If a rise in agglutinin titre of at least 100 per cent. is established in this way it may be taken as indicating a significant increase in antibody content.

### *Interpretation of Results*

From what has been stated in the preceding sections it is evident that the most important diagnostic criterion is the rise in OX19 titre during the attack and its fall during convalescence. When diagnostic conclusions are drawn from the result of a single agglutination test, complete agglutination of the standard suspension at 1:80 or 1:100 may be considered as significant, provided the patient has not been recently inoculated with typhus vaccine and is not a native of an endemic area. This degree of agglutination corresponds to "Total" in the scale employed in Dreyer's technique. If the patient has a history of inoculation with a rickettsial vaccine 2 or 3 months before the onset of his illness complete agglutination in 1:200 or over may be taken as strongly

suggestive of active infection. In endemic areas even higher titres may occasionally be found to be due to past infection. A marked increase in titre however established by repeated examinations at intervals of 2 days, is generally conclusive. Quite often the increase may be observed even after an interval of 24 hours.

On the other hand an unaltered titre of agglutination if established by repeated examinations throughout the whole course of an acute disease will reveal the non-specific or residual character of the reaction. This finding may, as a rule, be interpreted as serological evidence against the typhus nature of an existing fever, because complete absence of rise and fall in the OX19 titre is quite exceptional in louse borne typhus and occurs only in cases of extreme severity which usually end fatally. For this reason diagnostic significance can be ascribed to the negative as well as to the positive result of the test.

Although complete (Total) agglutinations in dilutions 1:25 and 1:50 are not decisive when obtained in the first examination of a patient's serum still, they ought not to be ignored in routine work. When found in a second or third examination in the course of the disease after an earlier negative result, these low-titre reactions are as decisive as those obtained in high titres. The low-titre reactions are of especial importance in the early diagnosis of cases, and have been employed almost universally ever since the test was first introduced. In recent papers published in this country and abroad the suggestion has been made that for practical purposes of typhus diagnosis any positive reading below the serum dilution 1:100 may be ignored and regarded as normal (VAN ROOYEN and BEARCROFT 1943). There is no reason whatever for this suggestion. The occurrence of low titre normal agglutinins in dilutions up to 1:100 was well known to the early workers but the means of differentiating these reactions from the specific responses in typhus fever was also known (WEIL and FELIX 1918). Table III shows that in a certain proportion of cases the maximum titre may never exceed or even reach the level of 1:100. If the dilutions 1:25 and 1:50 are not included in the routine test such cases are missed, and in other instances the serological confirmation of the diagnosis is unduly delayed. Most of the statements regarding the relatively late appearance of a positive OX19 reaction and the slight assistance derived from it in the early diagnosis of cases of louse borne typhus are obviously due to failure to pay attention to low-titre reactions.

In endemic areas it is often of great importance to discover whether an earlier illness was typhus or not and the OX19 reaction is employed for the retrospective diagnosis of missed cases especially the mild and atypical cases that occur quite often in adults and more often still in children. It is seen from the examples given in Tables II and III that the majority of cases of louse borne typhus show a high OX19 titre during the early weeks of convalescence and that a significant drop in titre may be demonstrated at that time by suitably spaced repeat examinations. After some months however

the fall in titre is no longer steep enough to be readily demonstrable. Those cases which showed a low-titre OX19 reaction during the attack cannot be detected by the test after they have recovered.

The OX19 reaction is also positive in cases of so-called inapparent infection which show no clinical symptoms whatever. Such cases are of especial epidemiological importance in countries where typhus is endemic. The diagnosis of these symptomless infections is based on the demonstration of a rising or falling OX19 titre.

#### SLIDE AGGLUTINATION TESTS

A rapid slide test for carrying out the OX19 reaction was recommended by WELCH (1937) in the U.S.A. and by CASTANEDA *et al* (1940) in Mexico. German workers have been employing this method extensively since the beginning of the present war and have published a great number of reports describing various modifications of the technique. The aim of all these modifications is to enable the test to be carried out under the most primitive field conditions, when no laboratory or even hospital facilities are available. Preserved suspensions of *Proteus* OX19 are distributed from central laboratories and the test is carried out by mixing a drop of finger blood, or of the separated serum, with a drop of the concentrated suspension. Some of the German military laboratories issue the OX19 antigen in the form of an alcoholized or formalized suspension, stained with methylene blue; others send out slides on which a number of drops of the concentrated suspension has been dried. Dried cultures of *Proteus* OX19 reduced to a fine powder are also employed. Another procedure is to collect the specimens on glass slides in the form of dry smears of whole blood and test subsequently by adding a drop of the antigen. The tests are read with the naked eye according to the intensity and rapidity of clumping and it is stated that the results compare favourably with those obtained with test tube agglutination.

The slide tests are employed in epidemiological surveys of large communities, and mild cases and inapparent infections may be detected by this means. The test is also used in rapid bedside diagnosis in field conditions. Some of the German workers accept the results of slide agglutination as final, while others employ the test as a preliminary to the customary tube test. Since the original papers on the subject are not readily accessible at the present time, the reader may be referred to a number of abstracts written by Sir JOHN MEGAW in the *Tropical Diseases Bulletin* Vol. 39 (1942), pp 372 and 611 and Vol. 40 (1943), pp 133, 529, 598 and 600. These simple tests seem to be very useful under the exceptional conditions which called for the adoption of the various procedures.

#### MURINE TYPHUS. TYPE OX19

Murine typhus, often but inappropriately called endemic typhus, has a world-wide distribution, and our fighting forces are likely to make contact

with the disease in the Mediterranean, the Middle East and the tropical and subtropical Far East (see Table I) This variety of typhus is transmitted to man by the rat-flea and usually causes only sporadic cases although outbreaks may occur when rat infestation is exceptionally heavy The disease runs a mild clinical course with a very low case fatality rate and does not, therefore constitute a serious menace The agglutination reaction with *Proteus* OX19 is found in murine typhus with the same frequency as in louse borne typhus that is in almost every case, and the two varieties of the disease can be differentiated serologically only by complement fixation or agglutination tests with rickettsial antigens (BENGTSON and TOPPING 1942 PLOTZ 1943 VAN ROOYEN and BEARCROFT 1943 STUART-HARRIS REITTE and OLIVER, 1943)

The statement is often made that the OX19 reaction is not as early a sign in murine typhus as it is in the louse borne variety It is, however obvious from the published data that there has been little occasion for studying the development of agglutinins in the early stages of murine infections The sporadic cases do not often come under observation early enough for adequate tests to be carried out in the manner illustrated in Tables II and III So far nearly all the workers with the exception of REITLER *et al* (1939) have failed to pay attention to the two types of the agglutinin curve referred to in connection with louse-borne typhus Such incomplete data as are found scattered throughout the extensive literature on murine typhus do however indicate that the two types of antibody response occur in cases of murine typhus and that the maximum titres are attained approximately at the time of defervescence SPARROW and MARESCAL (1940) who transmitted the disease experimentally to mental patients with a view to the production of therapeutic effects made very careful observations on the agglutinin curves in seven patients and found a significant rise in the OX19 titre as early as in cases of louse-borne typhus

Accidental infection in a number of laboratory workers in this country recently provided an opportunity for testing the question of the alleged late appearance of OX19 agglutinins in murine typhus. VAN DEN ENDE *et al* (1943) published a detailed account of these laboratory infections including the results of OX19 tests and concluded (page 330) Agglutinins either did not appear or did not increase in amount before the second week of the disease My own experience with tests carried out on some of these cases proved to be different. Five of the twelve patients in the series published by VAN DEN ENDE *et al* were examined according to the technique discussed in the present paper and the results obtained in four of the cases are shown in Table V The fifth case (Y) was ambulant throughout, had no febrile symptoms and is therefore not included in the table.

These four workers had received several courses of typhus vaccine including a murine vaccine but failed to show any OX19 agglutinin response. During the illness however all of them gave a significant OX19 reaction which,

as Table V shows, was demonstrable in three of the four cases well before the end of the first week. In fact, even the figures published by VAN DEN ENDE *et al.*, which were obtained by the use of a different but unspecified technique,

TABLE V

SHOWING *Proteus* OX19 AGGLUTININ TITRES IN FOUR CASES OF LABORATORY INFECTION WITH MURDER TYPHUS.

Name	Date	Day of Illness	Agglutination of <i>Proteus</i> OX19 Suspensions (Standards Laboratory Oxford).	Significant Rise in Titre first Observed on
A	9.10.41—before inoculation		50±	8th day of illness
	6.11.41—14 days after 2nd dose of alk-acc vaccine Batch A (epidemic)		50±	
	8.1.41—10 days after 2nd dose of rat-lung vaccine Batch E (murine)		50±	
	13.1.41—14 days after 3rd dose of alk-acc vaccine Batch C (epidemic)		50±	
	17.1.42		50±	
	19.1.42	4	50±	
	1.1.42	8	100±	
	26.1.42	11	1,000+	
E	9.10.41—before inoculation		5—	9th day of illness
	6.11.41		5—	
	8.1.41		25—	
	13.1.42		5—	
	20.1.42	3	25—	
	1.1.42	4	25—	
	23.1.42	6	5—	
	26.1.42	9	25++	
	29.1.42	12	50+	
	4.4.42	20	100±	
J	9.10.41—before inoculation		25 tr	8th day of illness
	6.11.41		5 tr	
	8.1.41		25 tr	
	13.1.42		5 tr	
	17.1.42	3	25 tr	
	19.1.42	5	50+	
	21.1.42	7	250±	
	26.1.42	1	500±	
L	15.11.41—before inoculation		50 tr	8th day of evening pyrexia (ambu last case)
	8.12.41—14 days after 2nd dose of rat-lung vaccine, Batch E (murine)		50 tr	
	27.5.42—21 days after 2nd dose of alk-acc vaccine Batch C (epidemic)		50 tr	
	1.6.42	1	50±	
	5.6.42	5	100+	
	8.6.42	8	200±	

tr = trace agglutination, visible by means of magnifying lens.

do not justify their conclusion since four of the six cases that are listed in their Table I showed an increase in titre on or before the 7th day and the remaining two cases were not examined at the right time-intervals to show that there was no significant rise before the end of the first week.

The conclusion, therefore seems justified that many cases of murine typhus can be diagnosed by the OX19 test during the first week of illness, provided the tests are carried out and interpreted in the manner already discussed in this paper

#### TICK-BORNE TYPHUS SEROLOGICAL TYPE UNDETERMINED

##### (a) FIÈVRE BOUTONNEUSE.

This variety of typhus is found in all the countries along the European and African shores of the Mediterranean and in the Balkans including Rumania. The disease is transmitted to man by the dog-tick *Rhipicephalus sanguineus* and is one of the mildest forms of typhus with almost no mortality. Unlike louse-borne and murine typhus cases of fièvre boutonneuse give irregular results in agglutination tests with the *Proteus* OX antigens. A significant reaction usually appears very late in the disease and the maximum titres reached are markedly lower than those in louse-borne and murine typhus. The serum of some patients with fièvre boutonneuse reacts only with *Proteus* OX2, or shows a higher agglutinin titre for OX2 than for OX19 (DURAND 1932 FELIX 1933b). Either of these results may as a rule, be interpreted as confirming the diagnosis of fièvre boutonneuse and also as excluding that of louse borne or murine typhus. When on the other hand, the predominant agglutinins are of the OX19 type a differential diagnosis cannot be made. Tests with rickettsial suspensions have not yet been reported in cases of fièvre boutonneuse.

DURAND (1932) very carefully investigated the course of the formation of *Proteus* OX agglutinins in a series of mental patients who were receiving fever therapy by means of induced fièvre boutonneuse. In the majority of his patients the maximum titres for either OX19 or OX2 were observed during the first 2 weeks after the defervescence in some cases the maximum titres were not attained until the 4th or 5th week of convalescence. According to the accepted criteria these late irregular and low titre agglutinins have been classed as group agglutinins, due to minor or group antigens present in the rickettsiae of fièvre boutonneuse, whereas the OX19 agglutinins in louse-borne and murine typhus are due to a major antigenic component of the corresponding rickettsiae (FELIX, 1933b).

##### (b) TICK BORNE TYPHUS OF INDIA

A tick borne typhus-like fever was first described from India by MEGAW (1917-1921) and some of the more recent observations have been analyzed in a careful study by BOYD (1935). So far the epidemiology of the disease-

and the behaviour of the causal rickettsiae in experimental animals have not been investigated. Consequently the type or types of agglutinin response to the *Proteus* OX antigens have not yet been established in cases of tick borne typhus in India. By analogy with what is known from the work on Rocky Mountain spotted fever (SPENCER and MAXCY 1930 DAVIS and PARKER, 1938) on the tick bite fever of South Africa (PIJPER and DAU 1930, 1931 1932) and on *fièvre boutonneuse*, it may be assumed that both the OX19 and the OX2 antigens are of equal importance in the diagnosis of the Indian variety of the disease. Whereas only these two antigens need be employed in routine work in the Mediterranean theatre of war in India the OXK antigen is also required, since cases of the OXK type of typhus have been reported from many parts of the country (MACNAMARA, 1935 BOYD 1935).

#### SCRUB TYPHUS (TSUTSUGAMUSHI) TYPE OXK.

Scrub typhus or *tsutsugamushi* is one of the major dangers to the fighting forces in the Far East. Since the OXK type of typhus was first identified in the Federated Malay States by FLETCHER and LESLAR (1925), it has been found that the disease is endemic in nearly all the tropical countries of the Far East (see Table I). The vectors are larval mites (*Trombiculae*) and the reservoirs of the infection are rats and field mice. The severity of the disease varies greatly in different localities and the case mortality is stated to vary from 1 per cent. to 60 per cent. A useful account of the clinical and epidemiological aspects of the disease has been published by LEWTHWAITE and SAVOOR (*Lancet* 1940).

Of the three *Proteus* OX strains only the OXK is agglutinated in cases of scrub typhus. Thus the test is not complicated by any group reaction to the OX19 and OX2 antigens. Nevertheless the technique and interpretation of the OXK reaction is fraught with difficulties which may be summarized as follows.

(1) Suspensions of *Proteus* OXK whether live or preserved, are more susceptible to non-specific normal agglutination by sera from man and experimental animals than are suspensions of OX19 and OX2 (FELIX, 1933a). The minimum titre of a significant reaction with OXK should, therefore be double the titre required in OX19 or OX2 agglutination. That is to say when a patient's serum is examined for the first time complete (total) agglutination at 1:160 or 1:200 may be taken as diagnostic of an active infection.

(2) It is more difficult to make a sensitive and stable suspension of the OXK strain than of the strains OX19 and OX2 (MARTIN 1931 BRIDGES 1944). Alcohol treated suspensions of OXK often show a certain degree of granularity and this tends to increase on storage. Non-specific agglutination of such suspensions may readily be obtained with relatively high dilutions of serum from patients who are suffering from various febrile diseases. The high-titre OXK reactions observed by VAN ROOYEN and BEARCOFT (1943) in a number of their cases of louse borne and murine typhus were most likely

due to this source of error. In another paper recently published from the Middle East (BROCKBANK and WHITTAKER 1944) it is stated that agglutination against *Proteus* OXK was not performed because the suspension of the strain was unreliable. Special precautions should therefore be taken to guard against this pitfall. The time of expiry of the OXK suspension should be made shorter than that of the OX19 and OX2 suspensions and the quality of each batch should be carefully checked by the inclusion of adequate controls in the tests.

(3) The OXK reaction is found positive in almost every case of scrub typhus if the serum is tested several times during the fever and early convalescence. In this respect the OXK reaction holds the same position in scrub typhus as the OX19 reaction does in louse borne and murine typhus. The maximum titres for OXK in cases of scrub typhus are also often as high as those for OX19 in the appropriate varieties of the disease provided that a sensitive OXK suspension is available. There is however a serious drawback to the OXK test, which is caused by the relatively late appearance of OXK agglutinins. Those who have had the greatest experience of scrub typhus in Malaya (FLETCHER and LESSLAR 1926, LEWTHWAITE and SAVOOR, 1940) and in Sumatra (WOLFF 1932) agree that a significant reaction is rarely observed before the second week of the disease and that the maximum titres are usually reached in the 3rd or 4th week. Thus the test is not an aid to early diagnosis. It should be noted, however, that an earlier appearance of OXK agglutinins has been reported in cases of scrub typhus in India (MACNAMARA, 1935, BOYD 1935). The workers in India employed preserved suspensions which had been prepared by BRIDGES (1935).

The technical details that have been discussed in connection with the OX19 reaction apply also to the OXK test. A rise in titre of at least 100 per cent. when established with a properly checked suspension may be considered as a significant reaction. If repeat specimens are examined at intervals of not more than 2 days it may be possible to confirm the diagnosis at a somewhat earlier stage during the disease. The agglutinin response in cases of scrub typhus has not yet been studied with sufficient precision to give an adequate answer to the question whether a relationship exists between reaction curve and clinical course similar to that which obtains in louse borne typhus. In studies of this kind special attention should be paid to what has been called the low titre reaction curve.

#### SUMMARY

Two different types of the curve of OX19 agglutinin formation are found in patients suffering from louse borne typhus. The two types of reaction curve are related to the clinical course of the disease and form the basis for the interpretation of the results of the Weil Felix test.



Rickettsial vaccines stimulate demonstrable OX19 agglutinins in a relatively high proportion of inoculated persons. The OX19 antibody response is of a moderate degree, similar to the O antibody response after T.A.B. inoculation.

Residual OX19 agglutinins, due to a previous attack of louse borne typhus, do not show significant fluctuation of the titre in the course of various febrile diseases. It may be assumed that the same holds for OX19 agglutinins produced in response to anti typhus inoculation. Residual O agglutinins for typhoid and paratyphoid bacilli, whether due to previous infection or inoculation also behave in like manner.

The technique of the agglutination test with preserved suspensions of *Proteus* OX19 is described. Repeated tests with low dilutions of serum including dilutions 1/25 and 1/50, are of especial importance in early diagnosis. Some of the possible sources of error are discussed.

The various modifications of a slide-agglutination test, now used by German workers for rapid diagnosis in field conditions, are briefly mentioned.

The following typhus-like fevers occur in the areas which at present are, or soon may become a theatre of operations, viz. murine typhus, "fièvre boutonneuse", tick typhus of India and scrub typhus. The *Proteus* OX reactions peculiar to each of these varieties of the disease are compared with the OX19 reaction as it is known in louse-borne typhus.

## REFERENCES

- BENNETT I. A. & TORRENO V. H. (1942). *Amer. J. publ. Hlth* 32, 43.  
 BIRD Z. (1924). *Zbl. Bakt. Abt. I Orig.* 83, 196.  
 ——— & SCIENTAG, F. (1917). *Munch. med. Wschr.* 64, 1409.  
 BOYD J. S. H. (1933). *J. R. Army med. Cps* 65, 289-361.  
 BRIDGES, R. F. (1935). *Ibid.* 64, 153.  
 ——— (1944). *Trans. R. Soc. trop. Med. Hyg.* 37, 343.  
 BROCKMAN, W. & WHITTAKER, S. R. F. (1944). *Lancet* 1, 150.  
 CASTANEDA, M. R. (1909). *Amer. J. Path.* 16, 467.  
 ———, SILVA, R. & MOSCOWITZ, A. (1940). *Rev. Med. Hosp. gen. Mex.* 9, 382.  
 ——— & ZIL, S. (1933). *J. exp. Med.* 58, 55.  
 COX, H. R. (1933). *Publ. Hlth Rep. Wash.* 53, 2241.  
 DAMM, G. J. & BILLINGS, F. T. (1942). *J. Immunol.* 44, 51.  
 DAVIS, G. E. & PARKER, R. R. (1938). *Publ. Hlth Rep. Wash.* 53, 15-5.  
 DING, E. (1943). *Z. Hyg. Infektkr.* 124, 670.  
 DURAND, P. (1932). *Arch. Inst. Pasteur Tunis*, 20, 395.  
 ——— & GIMOND, P. (1940). *Ibid.* 29, 25.  
 FELIX, A. (1916). *Wsch. kbn. Wschr.*, 29, 5-3.  
 ——— (1917). *Z. Immunforsch.* 29, 602.  
 ——— (1929). *J. Hyg. Camb.* 28, 418.  
 ——— (1930). *System of Bacteriology*, 7, 413. London: Med. Res. Counc.  
 ——— (1933a). *Trans. R. Soc. trop. Med. Hyg.* 28, 363.  
 ——— (1933b). *Ibid.* 27, 147.  
 ——— (1942). *Brit. med. J.* 2, 587.  
 ——— & GARDNER, A. D. (1937). *Bull. Hlth. Org. L. a. N.* 9, 223.  
 ——— & OLITZKI, L. (1929). *Brit. J. exp. Path.*, 10, 26.

- FLETCHER, W & LESLAR, J E (1925) *Bull. Inst. med. Res F.M.S* No 2  
 — & — (1926) *Ibid.* No 1  
 GARDNER, A. D (1929) *J Hyg Camb* 28 376  
 LEWTHWAITE, R. & SAVOOR, S R. (1940) *Lancet* 1, 255 305  
 LIU P Y & ZIA, S (1940) *Amer J publ. Hlth.* 30, 77  
 MACNAMARA, C V (1935) *J R. Army med Cps* 64, 174  
 MARTIN P H (1931) *Rep Inst. med Res., F.M.S* p 35  
 MEGAW J W D (1917) *Indian med. Gaz* 52 15  
 — (1921) *Ibid* 56 381  
 OKTINGER, W (1918) *Zbl Bakt. Abt. I Orig.*, 80, 304  
 PENFOLD J B (1944) *Brit med. J* 1, 114  
 PIJPER, A. & DAU H (1930) *Brit J exp Path.* 11, 287  
 — & — (1931) *Ibid.* 12, 123  
 — & — (1932) *Ibid* 13 33  
 PLOTZ, H (1943) *Science* 97, 20  
 REITLER, R. BISH S & MARBERG K. (1939) *Trans R. Soc trop Med Hyg* 33 197  
 SONNENSCHEIN C (1943) *Dtsch med. Wschr* 69 11  
 SPARROW H & MARECHAL, P (1940) *Arch. Inst Pasteur Tunis* 29 53  
 SPENCER, R. R. & MAXCY K. F (1930) *Publ. Hlth. Rep Wash.* 45 440  
 STUART HARRIS, C. H REITTE, G K. C. & OLIVER J O (1943) *Lancet* 2, 537  
 SUFFLE, K. & FISCHER, H (1943) *Arch Hyg Berl.* 129 158  
 VAN DEN ENDE, M HARRIS E H R. STUART HARRIS C. H STEIGMAN A. J  
 & CRUICKSHANK, R. (1943) *Lancet*, 1 328  
 VAN ROOYEN C R. & BEARCROFT W G C. (1943) *Edinb med J* 50, 257  
 WEIL, E (1920) *Dtsch. med Wschr* 46, 343  
 — & FELIX, A. (1918) *Munch. med Wschr* 65 17  
 WELCH, H (1937) *Amer J publ. Hlth.* 27 Suppt. 141  
 WOLFF G (1922) *Ergebn. Hyg Bakt.* 5, 532  
 WOLFF J W (1932) *Genesk. Tijdschr Ned Ind.* 72 896  
 ZLOCISTI T (1917) *Z. klin Med* 85 197



## NOTE ON THE PREPARATION OF SUSPENSIONS FOR THE WEIL-FELIX TEST

by

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In a paper published some years ago\* I described the details of the technique used in the preparation of alcoholized suspensions of the three *Proteus* OX strains that are employed in the Weil-Felix test. Certain changes in technique have been adopted subsequently and it may be useful to other workers to give a brief description of the procedure now followed in this laboratory.

Plate the *Proteus* OX culture to be used on plain agar. If the culture contains organisms of the spreading H+O form plate on phenol-agar (1 in 1,500) to ensure growth in single colonies. Incubate for 24 hours. Pick a number of colonies say six, each on to two agar slopes, and incubate 24 hours. The one slope is used for test the other is kept as "office copy".

Add about 2 ml. of saline to each test slope and wash off the growth. Pour off the suspensions into clean test tubes and fill the tubes about three-quarters full with 96 per cent. alcohol. Shake up all tubes thoroughly during the course of 1 hour. Remove the alcohol in the centrifuge and resuspend the organisms in 0.25 per cent. formal-saline. Reduce to suitable density for agglutination test.

Test all suspensions with the corresponding type serum and choose that which agglutinates most rapidly most completely and to the highest titre. The test is preferably carried out with typhus serum if available rather than with *Proteus* rabbit immune serum.

If the original culture is known to be in good condition the whole of the above may be omitted and the suspension prepared from the whole culture. But occasional colony selection is advisable.

Growth in bulk is carried out in Roux bottles or screw-capped "medical flats" which have been coated on one side with unfiltered agar. One broth tube (5 ml.) is inoculated from the office copy of the selected colony for each Roux bottle to be used. The broth tubes are incubated for 24 hours after which the contents are poured into the Roux bottles. The broth is allowed to flow over the whole surface of the agar and the bottles are then placed in the incubator with their necks slightly raised so that the broth is at one end.

After 24 hours incubation add a small quantity of saline and wash off the growth. Filter through cotton wool into one

\*BRIDGES R. F. (1935) *J. R. Army med. Cpr.*, 64, 153

capped bottles. Add 96 per cent. alcohol in the proportion of not less than 4 volumes to 1 volume of suspension. Shake up thoroughly during the course of 1 hour.

Suck off as much as possible of the supernatant alcohol and transfer the remainder containing the organisms to centrifuge tubes. Swing rapidly for a few minutes. Pour off the alcohol from the deposited organisms, removing the last drops with a pipette.

Resuspend the organisms in sterile saline solution and transfer to screw capped bottles. Shake up very thoroughly until it is seen that all clumps have been smoothed out and no granularity remains. Add 2 per cent. buffered formal-saline to make concentration of formalin 0.25 per cent. (i.e., add one seventh of the volume of suspension).

In the case of the OXK strain the alcoholized organisms should be resuspended in sterile distilled water *not saline* and all further dilution should be made with distilled water. But the 2 per cent. formalin may be added in the form of buffered formal-saline as in the case of the OX19 and OX2 strains.

Standardize the suspension by adding more sterile saline (distilled water in the case of OXK) and 2 per cent. buffered formal-saline (final concentration of formalin 0.25 per cent.) to a density equivalent to 4.500 million *Bacterium coli* per ml.

Note 1. 2 per cent. buffered formal-saline is prepared by adding the required quantity of formalin to a measured quantity of sterile saline and then bringing the pH to 7.6 by addition of  $\text{Na}_2\text{HPO}_4$ .

Note 2. In the Standards Laboratory we carry out the standardization of the suspension by means of an electric absorptiometer. But if Brown's tubes are used the following is a simple method —

Use only tube 3, since this is more easily matched than any other. One volume of suspension is diluted with volumes of saline until it is found to match tube 3. Then the amount of fluid which must be added to bring to the required density is equal to  $\frac{(a-37)x}{37}$  where "a" is the number of times that the suspension must be diluted to bring to the value of tube 3, and "x" is the volume of suspension to be diluted. Thus, supposing we have 50 ml. of suspension and it is found that it must be diluted with 11 volumes of saline, or twelve times, to bring it to the density of tube 3 then the quantity of fluid which must be added to give a concentration equivalent to 4.500 million *Bact coli* per ml. is equal to  $\frac{(12-37)50}{37} = 11\frac{1}{2}$  ml. This fluid is added as to seven-eighths in the form of sterile saline (distilled water in the case of OXK) and one-eighth of buffered formal-saline.

The figure 37 in both numerator and denominator of the above formula represents the number of times that the finished suspension is required to be denser than tube 3. It can be increased or diminished according as a stronger or weaker suspension is thought desirable.

## CORRESPONDENCE

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### THE TREATMENT OF TROPICAL ULCERS AND OTHER SKIN AFFECTIONS WITH LOCALLY PREPARED ACRIFLAVIN KAOLIN POWDER.

*To the Editor TRANSACTIONS of the Royal Society of Tropical Medicine and Hygiene*

SIR,

The necessary conservation of drugs such as zinc oxide, iodoform, bismuth, and liquid paraffin for the compounding of Z I P and B I P led me to exploit less costly and more easily obtainable material.

For the past 6 months at the Karonga hospital, I have used, exclusively and with good results, a preparation, A.K. powder made from a local kaolinitic earth, impregnated with acriflavin, in the treatment of tropical and other, ulcers and all skin affections which require an antiseptic emollient drying powder.

The crude masses of gritty earth are pounded in an African wooden mortar put in a 12 gallon drum and thoroughly stirred up in water. The washing may have to be repeated to recover the bulk of the clay. The supernatant fluid, containing the particles in suspension is poured off into another receptacle, and in a few hours an almost impalpable white clay is deposited, which is collected and fire-dried, and the hard cake thus obtained ground into powder.

Two soluble tablets, 1.75 grams each, of acriflavin dissolved in half a pint of water are mixed with half a pound of the powdered earth, which is again fire-dried and pulverized, when a fine sterile ochre-coloured product is obtained. In this district, 50 pounds of crude earth yield 4 of fine powder.

On reception the ulcer is irrigated with warm 1-1000 pot. permanganate lotion, and the A.K. powder dusted on with a dredger. A suitable piece of lint, wrung out in sterilized ground nut oil is superimposed and a bandage applied.

The irrigation and dressing is repeated every other day.

Patients express immediate relief from pain and discomfort on of the dressing.

Foul tropical ulcers are particularly benefited and clean up rapidly. The effect on chronic ulcers such as "veld sores" is striking.

When definite signs of healing appear the treatment described is discontinued, and ointments, equal parts of boracic and zinc oxide, later zinc oxide alone, are used to finish off with. Syphilitic and yaws ulcers, of course, require constitutional treatment as well.

Half a pound of the A.K. powder suffices for an average of thirty cases, and the saving in time and expense is considerable.

The method is simple and effective and has been introduced at the rural dispensaries in the district.

I have entered into some detail in order to save others similarly situated the trouble of experiment.

I am, etc.,

J. O. SHIRCORE.

Karonga,  
Nyasaland.

# TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

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VOL. XXXVII No 6 May, 1944

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ORDINARY MEETING  
of the Society held at  
Manson House, 26, Portland Place, London, W.,  
on

Thursday, 16th March, 1944, at 3 p.m.

THE PRESIDENT  
SIR HAROLD SCOTT K.C.M.G. M.D. F.R.C.P.  
in the Chair

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## PAPER

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HEAT EFFECTS IN BRITISH SERVICE PERSONNEL IN IRAQ

BY

T. C. MORTON O.B.E. M.D. F.R.C.P. Air Commodore R.A.F.  
*Institute of Pathology and Tropical Medicine R.A.F.*

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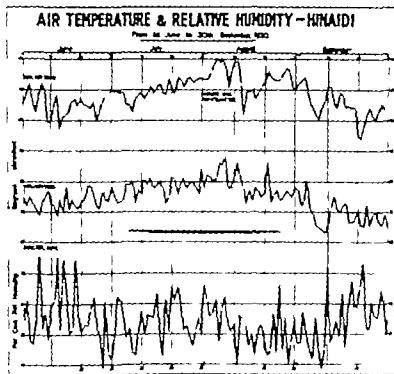
### CLIMATOLOGY

Iraq was aptly described by a British Tommy in the last war. As a country consisting of two ruddy long rivers and miles and miles and miles of sweet damn all. Apart from a thin fringe of cultivation bordering the rivers and canals, at few places more than a mile in width, the country consists of flat desert in the summer and weary miles of flooded countryside in March and April. In the winter the ubiquitous camel thorn and stunted desert shrubs veil the desert with a thin mantle of green and afford pasturage to the numerous camels, goats and fat tailed sheep of the nomad and semi nomadic tribes. The desert



does not consist of sand but of alluvial mud deposited by the floods. The prevailing tone is a drab khaki which reflects and radiates the burning rays of the sun and this panorama is varied only by salt pans in the low lying depressions. Southern Iraq is in reality a flat delta in Biblical times the two rivers, the Tigris and Euphrates, had separate mouths and the alluvial deposits carried down by them in the course of centuries have gradually built up the delta causing it to encroach on the Persian Gulf to such an extent that Ur of the Chaldees, once a flourishing sea port of Sumeria, is now some 160 miles inland.

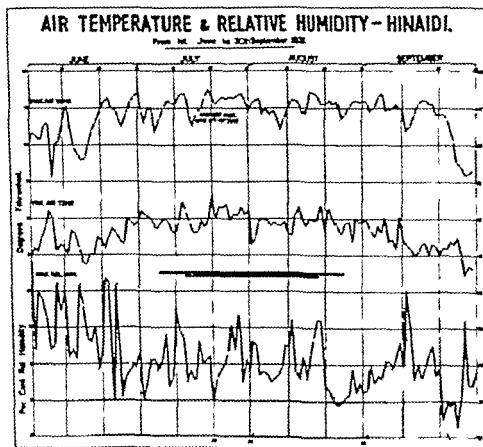
GRAPH 1



The main annual rainfall of Iraq is only 6 inches a year and is limited to 4 months from November to February. The hot season commences in May and continues until the end of September the last fortnight in July and the first fortnight of August being the hottest time of the year. The highest shade temperature for the last 15 years, as far as R.A.F. meteorological data record, was a temperature of 125° F at Mosul in northern Iraq. Fortunately the nights are relatively cool, the highest night temperature recorded during the 1930 heat wave was 88° F with a humidity of 42 per cent. on a day when the

shade temperature reached  $123^{\circ}\text{F}$ . The relatively cool nights even in the hottest months render Iraq a possible country for the white man living under good conditions though day temperatures of  $135^{\circ}$  to  $140^{\circ}\text{F}$  are not uncommon in Double Fly E P tents. A study of annual meteorological charts shows that severe heat waves tend to occur about every third year when for from 3 to 5 days the maximum temperature remains in the  $120^{\circ}\text{s}$  and as Sir WILLIAM WILLCOX (1920) recorded, it is the cumulative effects of heat that matter the greatest incidence of cases occurs on the third or fourth day of the heat wave and

GRAPH 2



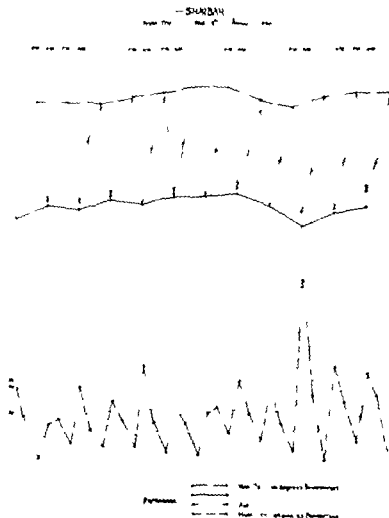
the individual frequently succumbs to heat effects in the night or early morning when the atmospheric temperature has fallen very considerably

### AETIOLOGY

Heat hyperpyrexia and heat exhaustion are due to a general parboiling or overheating of the blood and body tissues and not to any mysterious property in the rays of the sun in the tropics. The clinical syndromes resulting from overheating are by no means confined to the tropics. They occur in furnace

workers in temperate climates but owing to the men working in short shifts and then being removed to a cooler atmosphere the profound changes seen in endemic areas rarely occur as the break and return to a cooler atmosphere gives the body a chance to overcome the results of dehydration. Active service conditions

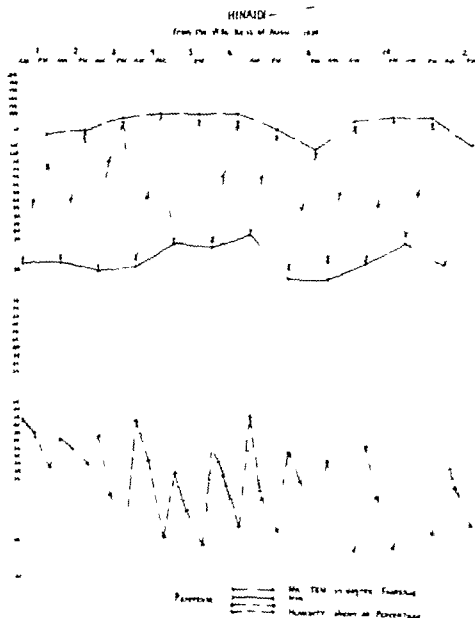
GRAPH 3  
MAXIMUM AND MINIMUM DAILY TEMPERATURE AND CORRESPONDING HUMIDITY



in countries such as Iraq especially when unsalted new reinforcements from temperate climates arrive in the middle of the hot weather always lead to an increased incidence of cases. Meteorological factors such as humidity play an important part as regards the suppression of sweating and the heat hyperpyrexia

syndrome will always be common in hot humid areas such as Basrah whilst heat cramps are more common in hot dry areas. The overheating of the body throws a strain on the heat regulating system and the heat loss occurs mainly through the sweat glands. It is interesting to note that it has been proved

GRAPH 4  
MAXIMUM AND MINIMUM DAILY TEMPERATURE AND CORRESPONDING HUMIDITY



that more sodium chloride is lost in the sweat of new arrivals to the tropics than in the acclimatized and recent experience has shown how important a role sodium chloride plays in the genesis of heat exhaustion and heat hyperpyrexia. It has been known for many years that the muscular cramps that stokers suffered

from could be prevented by the addition of salt to their drinking water but it is only within comparatively recent years that this observation has been applied to the tropics and the paramount importance of a sufficiency of salt and water for the maintenance of health been realized. Army experiments were carried out in India in 1938 and it was found that after a normal route march of 9 miles in the hot weather with a shade temperature of  $104.3^{\circ}\text{F}$  and a relative humidity of 47 per cent that the average salt loss ( $\text{NaCl}$ ) per man was 6.9 grammes and that the water loss amounted to between 6 and 8 pints, in addition LEMMON (1938) found in a 9-mile march at  $107^{\circ}\text{F}$  the loss during the march was 6.5 grammes of  $\text{NaCl}$  the blood chloride level being reduced from 500 mg to 417 mg per cent. In order to maintain efficiency in the tropics in the hot weather it is necessary to ingest about  $\frac{1}{2}$  to 1 oz. of salt a day normally the food contains half this amount so that the balance must be made good by extra salt. Ten grains of salt to a pint of cold water makes quite a palatable drink and considerable quantities of salt can be added to fresh or tinned tomato juice flavoured with a little Worcester sauce, which makes an appetising non-alcoholic cocktail before lunch. The universal popularity of well-salted almonds, pistachio nuts and chip potatoes, etc. in the tropics is a physiological craving that should be encouraged and made available to all ranks by being offered for sale at the wet canteens, sergeants and officers messes, etc. The fluid loss should be made good and, dependent on the amount of sweating and nature of the work involved the water intake required will vary from 1 to 2 gallons per man per day. In workshops the following drink\* should be readily available and men should be instructed to drink frequently but not more than 8 ounces at a time.

Sodium chloride	6 ounces	Seventeen fluid ounces of this con-
Potassium	4 ounces	centrated solution to be added to 3
Water	1 $\frac{1}{2}$ pints	gallons of water for drinking. A
		flavouring agent may be added

### BIOCHEMISTRY IN HEAT EFFECTS

The whole subject is in a condition of flux. The physiologists in the laboratory have attempted to over simplify the matter by such extreme subdivision that they have produced a classification of subclinical entities that is of little value to the clinician whose sole object is to make a correct diagnosis and institute the appropriate treatment. This problem awaits solution in spite of all the careful experimental work of Dr FRANK MARSH (1930) of the A I O C where the preventive measures adopted by that far-seeing company have been so successful that he is starved for human clinical material. I was delighted to hear that the War Office and Medical Research Council sent two investigators

\* For this I am indebted to DUNLOP, McNEIL and DAVENPORT. *Text Book of Medical Treatment*.

out to Iraq in 1943 and we await their report with great interest. My own attempts in this field were limited to chloride investigation of the urine and blood urea estimations. I found the urinary chlorides markedly reduced in all severe cases of heat exhaustion and in every case of heat hyperpyrexia. The blood urea was raised in one or two cases of prolonged heat hyperpyrexia but I could find no evidence of permanent renal damage due to heat effects *per se*. The critical assessment of electrolytic imbalance, whether alkalosis or acidosis is predominant in a particular case at a particular moment, is a matter for the biochemist but what the clinician wants is a method of treatment which will safely restore the disordered metabolism. A treatment which is too specific, for example alkalis to treat acidosis or ammonium chloride for alkalosis, is too dangerous unless the services of a well-equipped laboratory are at hand for one has learnt by experience how easy it is to swing from one extreme to another especially when the intravenous route is necessary. Fortunately in 0.9 per cent NaCl and 5 per cent glucose we have a safe and reliable therapeutic treatment readily available which if administered early will restore the disordered metabolism. Even in these days of facile intravenous therapy it is necessary to stress that even these simple solutions must be carefully administered and the intake and output charted if pulmonary oedema is to be avoided.

#### NOMENCLATURE.

There are three distinct clinical entities, although the dividing line between them is not absolute and borderline cases may occur.

##### 1. *Syncope*

This occurs in temperate climates in hot stuffy atmospheres and also in heavily overlaid soldiers on the march. The essential pathology is a temporary cardio-vascular collapse which, like other faints may progress to marked prostration with giddiness, a small soft fluttering pulse, shallow breathing, dilated pupils, a cold skin and subnormal temperature. On recovery the patient is bathed with a cold clammy sweat and severe headache and mental confusion may follow for a few hours. Death may occur in cases with heart disease. The urinary chlorides are not reduced.

*Treatment*—Dorsal decubitus in a cool place, the loosening of tight clothing and the bathing of the face with cold water together with the application of ammonia to the nostrils and a small dose of sal volatile.

##### 2. *Heat exhaustion*

This is a clinical syndrome tending to occur as a result of severe and usually prolonged exposure to high atmospheric temperatures and is characterized by collapse, profuse perspiration, low blood pressure, nausea and vomiting and in severe cases muscular cramps. The urine is invariably

diminished and chlorides both in the blood and urine are markedly reduced. The blood pressure is invariably low. The mouth temperature may be normal or subnormal but the rectal temperature is invariably raised to a moderate degree, 100 to 101 F. It is possible that some severe cases of heat exhaustion will, if untreated, go on to heat hyperpyrexia but as a rule the clinical picture remains true to type and the treatment is different. The prognosis, provided adequate treatment is given is excellent.

### 3. *Heat hyperpyrexia.*

The essential factor is the failure of the heat regulating centres with the suppression of sweating, once the temperature reaches 106° F coma and convulsions ensue and the mortality rate is very high. The urinary chlorides are reduced.

### HEAT EXHAUSTION

The following description is based on a personal experience of thirty severe cases of heat exhaustion encountered in Iraq in British personnel over a period of years. A general impression was formed that there was a certain type of individual who was particularly prone to develop heat exhaustion—the lean, anxious spare type with a low systolic blood pressure—he was usually a sedentary worker and in 33 per cent of cases was a strict teetotaler over 63 per cent of the cases had not completed their first hot season. An analysis of predominant symptoms recorded the following results —

	Per cent		Per cent
Dizziness	53	Suppression of urine	16
Vomiting	70	Androsia	10
Muscular cramps	26	Nausea	80
Constipation	43		

There were no fatalities amongst this series of cases so the prognosis, provided the condition is recognized and adequately treated, is excellent. In two cases it was necessary to recommend a transfer to a cooler climate. One of these cases was particularly interesting as although this patient had lived for over 10 years in the tropics this was his third attack and each attack had been sufficiently severe to necessitate the use of prolonged intravenous salines and on two occasions his life had been in jeopardy. His blood pressure was abnormally low for a man of 32. Systolic 103 diastolic 65 and I have noticed the same low blood pressure in several other cases.

### *Symptomatology*

In some cases the actual onset is sudden but there is usually a premonitory stage during which the patient suffers from anorexia, weakness of the legs, head ache and constipation for 2 or 3 days before collapsing. In many instances this collapse occurs at night and bears no relation to exertion. The patient at this

stage shows all the symptoms of shock, a low blood pressure, cold clammy and profuse perspiration and mental apprehension and irritability nausea and vomiting may ensue, the vomitus eventually becoming bile stained. In the severe cases violent cramps in the abdominal and leg muscles are a marked

CHART 1  
BAGHDAD AREA - HEAT EXHAUSTION  
CLINICAL FACTORS

Case	Temp on Admission	R	M	Blood Pressure on admission	Di33i	Nausea & Vomiting	Cramps	Constipation	Retention of urine	Duration of Fever	Notes
1	98°			88 46	-	+++	++	-	-	24 hrs	
2	101°			-	-	-	+	+		2 days	-
3	98°			132 98	-	+	-			Nil	
4	101°			90 50	-	+++		-	++	3 days	
5	100°			-	+	+	-			2	
6	98°			118 72	-	++	++	+	+	2	-
7	98°			-	+					Nil	
8	101°			-						24 hrs	
9	98°			-				++		Nil	
10	97°					+		+			
11	98°					+				24 hrs	
12	99°			-	-			++		2 days	
13	98°				+	+		+		Nil	
14	Subnormal			134 90	-	++		-		3 days	
15	99°			-	+	+				12 hrs	
16	99°			118 74	+	-				24	
17	99°				-	-		++		48	
18	101°				-			+		24	
19	101°				+	+			-	2 days	+
20	99°				+	+		-		Nil	
21	99°			128 80	+	+	+			7 days	
22	100°			-	+	-				24 hrs	
23	98°			101 -	+	+++	++	+	++	Nil	
24	101°			100 78	+	++				4 days	
25	-				+	+		++		Nil	
26	104°				+	++				48 hrs	
27	101°				+	+++	+	+	+	2 days (Therapeutic Suppression)	
28	99°			98 60	+	++	+	+	+	3 days	
29	100°			85 50	+	+	+	+		2	
30	99°			103 65	+	+	-	-		2	

feature of the illness and the urine is invariably diminished in quantity. The urinary chlorides are greatly diminished in all severe cases this is a most valuable aid to diagnosis. In the most severe cases there is retention and suppression of urine, only 1½ to 2 ounces of urine being drawn off by



in the 24 hours. An increase in the quantity of urine passed, together with an increase in the percentage of chlorides, is an early and favourable sign of recovery. The axillary and mouth temperatures are often normal but the rectal temperature is invariably raised, usually to about 100° F. Rectal temperatures should be charted 2 hourly as in one case the temperature rose suddenly to 105° F. This was accompanied by maniacal delirium which rapidly subsided when the temperature had been reduced to 102°. Surg. Lieut. MACLEAN R.N.R. (1943) has reported an interesting case of heat exhaustion complicated by tetany due to hyper-ventilation resulting from rapid respiration and it is easy to see how this complicating factor can arise especially in unacclimatized nervous individuals. I personally have not encountered it. If the patient responds to treatment and the vomiting and cramps disappear a slight pyrexia appears which lasts for 2 or 3 days. In some cases headache persists for a week or 10 days after all other symptoms have disappeared.

#### TREATMENT OF HEAT EXHAUSTION

These cases should be nursed in the coolest ward in the hospital where an air-conditioned ward was available it was found that a temperature of 75° F. was the ideal temperature to maintain in the ward. Those cases with low blood pressures and symptoms of shock should be treated in the usual way by raising the foot of the bed, care should, however, be taken in the application of hot water bottles, and once the primary condition of shock has been relieved no further heat is to be applied for fear of creating a vicious circle. Hot coffee with plenty of sugar has been strongly recommended by R.A.F. medical officers at this stage, but I personally have had no experience of it. An enema of normal saline should be given if necessary, but purgatives are to be avoided as they increase the dehydration. Copious fluids containing glucose and sodium chloride (20 grains to the 9) should be given by the mouth, but if these are not retained or if the clinical condition warrants it intravenous NaCl 0.9 per cent. should be given by a saline drip the intake and output of fluids should be carefully charted and, as previously mentioned, an increase in the urinary output and an increase in the urinary chlorides are the earliest and most reliable signs of recovery. In certain cases an alkalosis develops from excessive vomiting and as Professor NORM MORRIS (1943) has pointed out the vomiting leads to loss of fluid which contains sodium with a great excess of chlorine. Accordingly carbonic acid is retained in the body fluids to satisfy the demands of base and an alkalosis is produced the kidneys promptly respond by excreting an alkaline urine with excess of sodium bicarbonate. If the alkalotic condition persists long enough the continuous excretion of sodium causes too great a reduction in the osmolar concentration of plasma and tissue fluids. The osmotic pressure is more important than the pH and the kidneys conserve the sodium even although by so doing the alkalosis increases in intensity. Accordingly the urine now contains a relative excess of organic acids with the result that its reaction

is acid while a state of intense alkalosis exists in the body. If now, sodium chloride is supplied in sufficient amount the kidneys can immediately return to their task of diminishing the alkalosis without running any risk of imperiling the osmotic pressure of the tissue-fluids and the urine becomes alkaline. In 1930 I treated with success several cases of heat exhaustion with 21 per cent bicarbonate of sodium in normal saline, together with glucose by mouth or intravenously (MORTON 1932). In 1939-1942 I attained even greater success with the use of sodium chloride, 0.9 per cent alone together with glucose and I am now firmly convinced that the good results obtained in 1930 were due to the sodium chloride and that the sodium bicarbonate is unnecessary and contra-indicated. If acidosis is present due to impaired renal function the best solution to use according to Professor NOEL BAKER, is m/6 sodium lactate (1.8 per cent.) The lactate is rapidly oxidized to carbonate, thus enabling the sodium to combine with the excess acid substances and carry them off to be excreted in the urine.

To sum up 0.9 per cent sodium chloride is the sheet anchor in the treatment of heat exhaustion together with glucose by the mouth or intravenously in order to provoke a diuresis and to treat the starvation the majority of these cases are suffering from and which if untreated may go on to acidosis.

#### DIFFERENTIAL DIAGNOSIS OF HEAT EXHAUSTION

Malignant tertian malaria and food poisoning may cause confusion but parasites are usually easily found in the algid syndrome of malignant tertian malaria and in food poisoning diarrhoea is constantly present. An estimation of the urinary chlorides will clear up the diagnosis in doubtful cases of heat exhaustion as they are always markedly diminished. Fantus test for a rapid estimation of urinary chlorides is worth carrying out as a routine on all cases admitted to a medical ward during a heat wave. In one case of this series although the vomiting ceased as a result of treatment, the temperature continued to rise and *Bacillus typhosus* was isolated from the blood on the fifth day. There is really an even greater risk of missing a surgical condition during an epidemic of heat exhaustion. a case of intestinal obstruction was admitted to a medical ward fortunately the projectile vomiting led to its early recognition.

#### HEAT HYPERPYREXIA.

The following description is based on a personal experience of eleven severe cases of heat hyperpyrexia encountered in British personnel over a period of years. A general impression was formed that there was a certain type of individual who was particularly prone to develop heat hyperpyrexia the obese thick necked chronic alcoholic with a high systolic blood pressure the average age of the patient was higher than in the heat exhaustion series and the mortality was 27 per cent. In the case of those individuals who did not conform to this description there were as a rule complicating factors such as

CHART 2.

## HEAT HYPERPYREXIA — CLINICAL ASPECTS

CASE No	1	2	3	4	5	6	7	8	9	10	11
Date of admission	AUG 1930	AUG 1930	AUG 1930	AUG 1930	AUG 1930	AUG 1930	AUG 1930	JULY 1931	JULY 1931	JULY 1931	JULY 1931
Prodromal malaise											+
Anidrosis			+								
Constipation											
Temp on admission, rectal		103°	103° 104°	103°	100°			106° 107°	104° 105°	104° 105°	105°
Highest temperature recorded		109°	108°	107°	107°	108°	108°	107°	105°	108°	109°
Delirium			+			+					
Coma											+
Convulsions											
Pupils		Dilated	Dilated	Dilated				Contracted	-		Dilated
Tongue furred		+						+			
Vomiting											
Suppression of urine		-									
Incontinence			+		-						+
Duration of fever		4 days Shed fever 10 days	4 days Shed fever 10 days	4 days Shed fever 10 days	5 days Shed fever 10 days	5 days Shed fever 10 days	5 days Shed fever 10 days	5 days Shed fever 10 days	10 days Shed fever 10 days	10 days Shed fever 10 days	10 days Shed fever 10 days
Result	Died	Died	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Died

malaria, urinary infection, oral sepsis and extreme physical exhaustion, etc. There was only one testotaller in this series and four of the patients were chronic alcoholics. An analysis of predominant symptoms revealed the following results —

Prodromal malaise, 100 per cent. frequency of micturition, one case only.  
Anidrosis, 100 per cent.  
Constipation, 18 per cent.  
Delirium, 46 per cent.  
Coma, 63 per cent.

Vomiting 54 per cent.  
Reflexes: Knee jerks lost in 30 per cent diminished in 70 per cent.  
Convulsions, 46 per cent.  
Hyperpyrexia, 100 per cent (criterion a temperature above 104.5 F)

Stertorous breathing present in all comatose cases.

Urinary chlorides were invariably diminished in all cases where it was possible to obtain a specimen for quantitative examination. This has also been recorded by Dr FRANK MARSH of the A.I.O.C. at Abadan. The general appearance of these patients was as a rule characteristic, the face was flushed, in some instances cyanosed, a dry burning skin was a constant feature and the blood pressure was usually raised. The onset was acute, in some cases the patient being admitted delirious, stuporous or in coma, and it was found that the more acute the onset the better the patient responded to thermantidote measures and the less tendency there was to relapse. If the temperature reached 108° F delirium and coma inevitably followed and it is doubtful if the temperature has remained at 108° F or over for more than 2 hours if recovery is possible, although short periods at much higher temperatures such as 110 to 112° F have been followed by recovery (*Notes on Effects of Heat*, 1943). I once saw a dying case of typhoid in the fourth week of the disease in Iraq whose temperature rose again and again to 112° F and it was pathetic to watch the frenzied strivings of the man's sweat glands to deal with the situation his eye sockets filled time and again with sweat which literally poured off his body in streams. Such an appearance is never seen in heat hyperpyrexia the hot, dry roughened skin, the bounding pulse, the flushed cyanosed face with congested conjunctivae of the typical acute case once seen is stamped indelibly in the memory. My limited experience fully confirms Colonel HEARNE's (1932) observation as to the value of the dry burning skin as an early sign of oncoming heat hyperpyrexia, and nursing orderlies should be trained to look out for it whilst recording pulse and temperatures a mere palpation of the thorax or axilla is sufficient. In the majority of the cases the temperature had settled to normal by the end of the week but in three cases a prolonged pyrexia associated with a furred tongue and a polymorphonuclear leucocytosis persisted for from 10 to 14 days. All laboratory investigations including blood cultures, agglutinations, etc. were completely negative and the temperature only settled down after prolonged residence in an air conditioned ward. Two cases were transported by air from Basrah to an air-conditioned ward in an R.A.F. hospital and it was amazing how these symptoms disappeared and their temperature fell to normal within 4 or 5 days whereas all previous thermantidote measures at Basrah had had no lasting effect. This enteric like syndrome is very confusing if not recognized and a perusal of old hospital records showed that similar cases had occurred in previous heat waves and that a relative and absolute polymorphonuclear leucocytosis for which no cause could be found was a constant finding in this type of case.

#### TREATMENT OF HEAT HYPERPYREXIA.

The temperature must be brought down as quickly as possible to 103° or 102.5° F by sponging with iced water and the use of fans. It is to eliminate malignant tertian malaria and in any doubtful case quinine is indicated. In one of the fatal cases in this series, although no

parasites could be found, intravenous quinine had been given and postmortem, malarial pigment was present in sections from the liver and spleen although no malarial parasites were found in smears from the brain and spleen. A temperature of 60° F was maintained in the air-conditioned heatstroke centre but as soon as the thermantidote measures had taken effect the case was transferred to the treatment ward which was maintained at 75° F as lower temperatures led to undue chilling of the patient and even at this temperature a blanket was appreciated. The patient was encouraged to drink large quantities of fluid containing NaCl and glucose but intravenous salines were not required in the hyperpyrexial type of case unless vomiting was troublesome, and in my experience they are rarely required as these cases are not usually dehydrated. Before resorting to intravenous saline it is essential to be guided by the systolic blood pressure haemoconcentration, etc. otherwise one may do more harm than good by overloading a failing circulation. The nursing was considerably eased by the provision of the air-conditioned wards and in no case was a second cold sponging necessary a welcome contrast to our experience in the 1930 epidemic, when for 10 days in one patient the rectal temperature rose to 108° F from one to three times in the 24 hours, necessitating repeated ice sponging and throwing a very heavy burden on the nursing staff. The question of iced enemas is a very vexed point they are of value under active service conditions where water and ice are scarce such as staging posts and on desert convoys, and here an iced enema of 0.9 per cent. normal saline is definitely indicated but by using them one deprives oneself of the recording gauge of the thermometer in the rectum and therefore we did not use them in our hospitals. Theoretically they are liable to increase shock. Convulsions and venous congestion were treated by venesection, about 15 ounces of blood being withdrawn with benefit and oxygen was administered when necessary. In one fatal case lumbar puncture controlled the convulsions and the fluid was found to be under pressure but otherwise normal, the patient eventually succumbing to circulatory failure. The use of a magnesium sulphate enema to relieve headache in convalescence was found to be of considerable benefit particularly in those patients whose cerebration was slowed and in whom there was no evidence of dehydration. Lumbar puncture except as a means of diagnosis in doubtful cases, is not recommended as a routine measure. The transition from the air-conditioned ward to an ordinary ward should be a gradual one. Neglect of this elementary precaution in one case of heat exhaustion led to a relapse necessitating further intravenous saline therapy. We found that it was better to let the patients sleep in an ordinary ward at night once convalescence was well established, and the hours spent in the air-conditioned ward were gradually whittled down to zero prior to discharge from hospital.

### PROPHYLAXIS

1 *Acclimatization* The principle of continuing troopings to the cool season so that newcomers gradually become acclimatized to the heat is an

excellent one any departure from this rule is fraught with danger but under war conditions is often unavoidable. It is essential that medical officers on troopships proceeding to the tropics should be familiar with the prevention and treatment of heat effects. Incoming drafts should be disembarked in the early hours of the morning or in the evenings and the removal of heavy baggage etc. should be carried out by acclimatized working parties and not left to the newcomer rendered soft and flabby after weeks of confinement on board a crowded transport.

2. *Air Conditioning* In certain hot localities in the Persian Gulf this is available for only 25 per cent of the personnel but it is possible to so stagger the working hours that all the men can spend some hours off duty in an air-conditioned room. This will on the analogy of the furnace worker in temperate climates, do much to prevent the cumulative effects of heat and enable the body to repair the results of disordered metabolism.

3. *Propaganda During the Hot Weather* The slogan "Drink more water. Eat more salt" was posted in all dining halls at the beginning of the hot weather. In addition to this, during a heat wave in July 1940 when for over 5 days the temperature was over 120° F. medical officers made a point of seeing that extra salt was added to the dietary and that men were warned to avoid getting constipated. Working hours were adjusted so that men started work an hour earlier and stopped work at 11.30 a.m. and frequent inspections were made of welding shops, tinsmith shops, etc. Persian coolers were installed in these workshops containing an ample supply of cool water to which salt was added and the men were encouraged to drink "little and often." As a result of these measures only two cases of heat exhaustion occurred a great improvement on our 1930 experience during an identically similar heat wave. The year 1941 in which active operations occurred in Iraq, Syria and Persia, was fortunately one of the coolest summers on record and it was owing to this meteorological blessing that we were spared a repetition of the 'Mesopotamia' of the last war when at the first battle of Ramadi over 300 cases of heatstroke occurred in one afternoon. In the hot summer of 1942 a severe outbreak occurred after I had left Iraq and I am hoping that some of our R.A.M.C. colleagues here may give us the benefit of their experiences.

#### SUMMARY

1. The division of heat effects into heat syncope, heat exhaustion and heat hyperpyrexia is advisable as although borderline cases do occur the clinical picture is as a rule clear-cut and the prognosis and treatment are radically different.

2. *Heat Exhaustion* Electrolytic imbalance and dehydration appear to be of primary importance in the genesis of heat exhaustion. The lean, spare type with a low systolic pressure is particularly prone to heat exhaustion and the age group is lower than in the heat hyperpyrexia cases. The quantitative

estimation of the urinary chlorides is a simple and reliable test in the differential diagnosis of these cases and in sodium chloride and glucose we possess a safe and effective remedy.

If intravenous therapy is indicated this must be controlled by charting the intake and output and estimating the haemoconcentration, otherwise there is a risk of pulmonary oedema. The prognosis in heat exhaustion is excellent provided the condition is recognized in time and adequately treated, otherwise cases may die of circulatory failure or go on to heat hyperpyrexia.

3 *Heat Hyperpyrexia*. This is always a grave syndrome the mortality is usually at least 30 per cent and may be considerably more. Alcohol and age are accessory and adverse factors and the condition is more frequent in the fat and plethoric. The essential factor is the failure of the heat regulating centre with the suppression of sweating although in the more protracted cases it is probable that an auto-intoxication is responsible for the prolonged pyrexia. Therapeutical measures and the nursing of these cases in artificially cooled wards are the basis of treatment.

4 *Prophylaxis*. (a) Ample cool drinking water containing 10 grains of sodium chloride to the pint, together with a total consumption of at least 1 ounce of sodium chloride a day is a paramount necessity in all endemic areas during the hot weather. (b) The provision of air conditioned or artificially cooled wards in hospitals in endemic areas is as essential as the provision of a well equipped operating theatre.

#### REFERENCES

- Field Service Hygiene Notes, India* (1940) Para 337  
 HARRIS, K. G. (1932) Hyperpyrexial heatstroke: a Mesopotamian experience with some aetiological views and a method of prevention arising therefrom. *Med J Aust* 10th year, 1: 228  
 MACLEAN, K. S. (1943) Observations on sunstroke and heat exhaustion in the tropics. *J R neu med Soc* 29: 31  
 MARSH, F. (1930) The etiology of heatstroke and sun traumatism. *Trans R Soc trop Med Hyg* 24: 257  
 ——— (1933). Further studies in heatstroke. *Ibid* 27: 255  
 MORRIS, N. (1943) Dehydration. *Lancet* 2, 91  
 MORTON, T. C. (1932) The aetiology and treatment of heat exhaustion and heat hyperpyrexia with special reference to experiences in Iraq. *Proc R Soc. Med* 25: 1263  
*Sth Afr Digest War Med* (1943) Notes on effects of heat for medical officers on troop ships. Persian Iraq Command. G.H.Q. 3: 2  
 WILLCOX, W. H. (1920) The nature, prevention and treatment of heat hyperpyrexia, *Brit med J* 1: 392

#### DISCUSSION

Colonel A. Sachs. Air Commodore MORTON's paper is of particular interest to me as I arrived in Iraq just about the time he was leaving. It therefore forms a valuable basis for comparison with the observations made during the hot weather of 1942 and 1943 and I hope that mine will be complementary to his own. As Assistant Director of Pathology I had the opportunity of

touring Persia and Iraq and visiting hospitals where cases were treated under different conditions.

It was found that seasoned troops in good physical condition attained a high degree of resistance. Indians were not immune, but although the incidence among them was lower than in Europeans the case mortality was higher. Gurkhas need the same degree of acclimatization as Europeans.

Among important *predisposing factors* not usually stressed were lack of sleep and rest, insufficient food prior to a move, and poor physical condition caused by fatigue or by some previous illness e.g., malaria, sandfly fever, dysentery, diarrhoea and sea sickness. Illnesses associated with high fever or persistent vomiting were particularly dangerous. It was found in workshops in the desert that by making *réveillé* later and so allowing an extra hour's sleep the men kept fitter and moreover there was no fall in output although the daily period of work was reduced by 1 hour.

A group of cases which does not appear to fall into any of the types described is *sub-acute effects of heat*. In the *apyrexial* or nearly *apyrexial* stage these cases were at first not recognized and were only diagnosed when they developed *hyperpyrexia*. They did not respond to treatment as well as acute heatstroke in a previously healthy individual. Diagnosis was difficult in the pre *hyperpyrexial* stage as the symptoms were similar to other illnesses.

The common early symptoms were headache, feeling of exhaustion or off colour, giddiness, constipation or diarrhoea and anorexia. Not infrequently there was a change in the patient's normal behaviour e.g., dullness, irritability, restlessness, or even insubordination. This stage may last from 3 days to 3 weeks but it was usually 2 to 10 days before *hyperpyrexia* developed.

In the mild early cases rest in a cool atmosphere, with plenty of salt solution to drink, is all that is necessary. In the more severe cases a cool atmosphere is essential, but these cases also require treatment for the marked dehydration and salt deficiency.

If in the early stage treatment is inadequate symptoms, although they may have passed off, are liable to recur on exertion or re-exposure to heat.

A deterioration in the patient's mental condition which may be *manic*, not infrequently develops with the *hyperpyrexia*. Coma and *convulsions* sometimes appear. The problems of treatment are those of *hyperpyrexia*, but a large proportion of these cases died in from 1 to 4 days after the onset from circulatory failure and bronchopneumonia.

#### PATHOLOGY

After perusing postmortem reports and examining sections from fatal cases which occurred during the hot weathers of 1942 and 1943 it was possible to record certain constant observations.

The first group consisted of cases of *hyperpyrexia*, who had died prior to the institution of intravenous treatment.



*Macroscopically*

The temperature of the body is high and in some cases apparently rises. In one case a rectal temperature of 115° F was recorded 3 hours after death.

Postmortem rigidity occurs unusually rapidly often within 1 hour and passes off much sooner than normal, i.e., within 6 hours.

On opening the body the peripheral vessels are found to be engorged with dark and viscid blood, such as is seen in peripheral circulatory failure.

The cerebral vessels are similarly engorged and form a red network over the brain. The pia mater shows signs of oedema.

Petechial hæmorrhages in the brain and small subpleural subpericardial, subendocardial and subperitoneal hæmorrhages have been observed in the majority of cases.

The mucous membranes of the stomach and upper part of the small intestines are so intensely congested that acute gastro-enteritis or even an irritant poison may be suspected.

The condition of the heart is generally characteristic. This is stony hard to the feel. It is believed that this is due to intense postmortem spasm of the myocardium.

The lungs are very hæmorrhagic and congested, and exude a blood stained froth, which is also found in the air passages.

*Microscopically*

*General Findings.* Degenerative changes of the parenchyma cells of the heart, liver kidneys and suprarenal occur early and have been found in post mortems carried out within 2 hours after death. After 24 hours the cellular element of the tissue has completely disappeared. This, to the inexperienced, would suggest acute antemortem necrotic changes in the liver kidney and pancreas. In view of the rapid early postmortem degeneration, it is impossible to decide whether antemortem damage has in fact occurred. The degeneration and "cooked" appearance of the organs is very characteristic.

Generalized engorgement of the vessels is a constant feature.

The presence of coarse granular pigmentation throughout the organs is suggestive of increased destruction of the red blood corpuscles. The cause of this is debatable.

*Brain.* The vessel walls are swollen and have a hyaline appearance. It is probable that this change is partly degenerative, and partly physical as a result of an alteration in the osmotic pressure of the plasma. (A relative increased plasma protein content follows dehydration.)

Oedema is marked. This is both perivascular and perineuronal.

The Virchow Robin spaces are often filled with a pale acidophilic staining fluid. Sometimes R.B.C.s appear to have migrated through the walls. This is suggestive of increased permeability of the vessel walls to fluid and cells.

Varying numbers of small hæmorrhages occur. In these areas the surrounding tissue is sclerosed. Thrombosed capillaries are frequently seen.

Chromatolysis occurs but again it is impossible to determine whether this is a postmortem or antemortem change.

*Lungs*—The alveolar walls show the presence of haemorrhagic oedema. These changes appear to be sufficient to reduce the capacity of the air sacs which results in a diminished vital capacity of the lung. The findings are very similar to those observed in early cases of phosgene gas poisoning and are very characteristic.

*The second group were treated cases of heat hyperpyrexia*

In the main, findings are similar to the untreated cases but depend to some extent on the quantity and rate of fluid given intravenously as cases of heatstroke are found to be particularly liable to develop pulmonary oedema.

When infusions have been given too lavishly there is an increase of fluid in the serous cavities, and some oedema occurs in the kidneys liver and gut. The lung tissue is more severely damaged than in the untreated case. Marked pulmonary oedema is always present, and signs of bronchopneumonia are frequently seen.

In the brain there is an increased cellular content, probably due to proliferation of the neuroglial and microglial cells.

*The third group were cases of effects of heat without hyperpyrexia*

This group consists of individuals who have been unable to acclimatize themselves. Hyperpyrexia is not a feature. Very often there is some underlying physical defect, or the condition may be a sequel to a previous illness due to effects of heat.

In these cases findings are modified. Fatty changes in the liver and heart, or signs of previous renal damage are superimposed.

*Commentary*

Some of the postmortem changes are undoubtedly due to physiological processes which are a sequel to the water and electrolyte loss. An impairment of the circulation follows the haemoconcentration, raised viscosity of the blood and the altered osmotic pressure of the plasma proteins. Eventually there is peripheral circulatory failure of which signs are found both during life and postmortem.

It would appear that in the stage when haemorrhagic oedema of the lung has occurred the vital capacity is diminished, and some interference with the  $O_2$  and  $CO_2$  exchange must take place resulting in a condition of anoxaemia. This view is supported by the beneficial results obtained after oxygen administration in severe cases.

It is thought that there may be an important relationship between the anoxaemia and the morbid histological changes described.

As Air Commodore MORROW has remarked, our knowledge of the biochemistry of the condition is in a state of flux, and until this is understood it is unlikely that there will be any great advances in treatment.

**Lt-Col. Robert Drew** I have been most interested in Air Commodore Moxton's valuable paper and I fully agree with him as to the predisposing causes. Most of the cases of heat hyperpyrexia seen by me were suffering from some intercurrent disease like malaria. Some of them were in hospital under observation or treatment in the dysentery wards and one patient who was being treated with atropine for a duodenal ulcer developed heatstroke. I remember seeing a patient with tetany similar to that described by Surg. Lieut. Maclean. The highest rectal temperature in the cases I have seen was 113° F and in spite of this the patient recovered, though he had considerable mental impairment afterwards.

With regard to acclimatization do people lose less sodium chloride in their sweat after living in a hot climate? I am not convinced by the evidence so far produced that acclimatized people lose less salt in their sweat. We are familiar with the work done by the Germans in this war on acclimatization. They put many of their soldiers into hot houses for a month before sending them to North Africa, so as to accustom them to the heat, and few diseases due to heat occurred in this group. Although, in the Army we provide salt tablets and give as much salt and water as possible to the troops during the hot weather I consider that acclimatization is a most important factor.

**Prof. P. A. Buxton** Those who have seen something of heatstroke and the effects of heat in the Persian Gulf will be glad to have heard Air Commodore Moxton put the modern view of the subject so clearly and well. Perhaps the most remarkable thing about his paper is the omission of all reference to sinuses, red shirts spine pads and topcoats. His total omission of those superstitions is a very encouraging thing because one sometimes feels how slow the advance of medical knowledge and its applications may be.

A minor point to remember is that after a grave operation the risk of heat stroke is increased by bandaging and dressing. Lives have been lost because those responsible for surgical cases have not been informed of this risk.

I would rather look forward than back in relation to this problem of the unfortunate effects of heat, and I wonder whether we British are going to make sufficient use of air conditioning? The Americans are already far ahead of us in the construction of barracks for the housing and comfort of troops in the tropics. Already in America on the eastern seaboard the use of air conditioning is commonplace in the hot months in hotels and offices. Conditions are trying there, but nothing approaching to what they are where our men are serving now and may live after the war. Very serious attention should be given to the liberal provision of air conditioning in barracks (not only in a few wards) in those areas, but I am rather afraid it will not be done.

Colonel S. P. James said that Professor Buxton's remarks led him to ask a question. He had listened last week to a broadcast on the modern war training

of British troops in India. He had heard with surprise that the medical authorities in India have drastically changed their ideas as to what can and cannot be done without injury to health under the fierce Indian sun. The broadcast said that the old-fashioned picture of troops protected by sun-helmets and spine-pads should be forgotten and that the topee was dead.

The question he wished to ask was whether, in fact the medical authorities in India have modified their views so drastically and if so whether the new views are also held in Iraq and other tropical countries?

What are the reasons for the new practice? The broadcaster seemed to think that 'pride' and "fashion" had something to do with the change. He said that the men live mostly stripped and that they are very proud of getting beautifully sun-browned. He said, the really fashionable wear is the hat, Gurkha felt \* which is worn at all possible times and in all possible ways.' A favourite way of wearing it was with the crown pressed down in the middle rather like the Homburg hat or like the tyn felt hat in which Mr WINSTON CHURCHILL used to be pictured by the cartoonists of 30 years ago. Colonel JAMES ventured to say that if fashion was a chief reason for the change in headgear and other kit, the British troops under training in India did not seem to him to be quite up to date. To be really in the fashion they should study a recent photograph of Mr WINSTON CHURCHILL that was published on page 62 of the Ministry of Information's booklet *The Eighth Army*. The photograph was taken during the PRIME MINISTER'S visit to Alamein in August. He is wearing a Cawnpore topee with a wide brim dark sun glare spectacles, a battle-dress tunic and gloves. He is carrying in one hand a fly-whisk, in the other a white umbrella. The photograph doesn't show whether his tunic is lined with red or whether it has a spine pad, but the whole outfit in every other respect is precisely what was strongly advised by the medical authorities in Mesopotamia in the last war.

Is it true that all these excellent precautions against the sun are only the bogies of old fogies which have now been abandoned?

And about acclimatization is it the present view that by continually exposing a man's bare head and his naked body to the fierce Indian sun he becomes immune to heatstroke? In this connection he would like to mention an example of heatstroke which occurred in Mesopotamia during the last war. Many will remember the practice adopted in that war of sending civilian specialists from England to various fronts to advise on medical and surgical arrangements and to send home reports of what they saw. With one of the several "Commissions" which visited Mesopotamia in 1916 there came a famous brain surgeon. He was by no means a young man, but he had all the

\* Experiments on the comparative efficiency of various types of sun-helmets and hats were described by CORSON in 1926 (*J trop Med [Hyg]* 29, 2) and by GLOVER in 1942 (*J trop Med [Hyg]* 36, 5). The single felt hats such as the Gurkha hat, were found to be the least efficient of all types tested.

new fangled notions which prevailed among some very young folks in England at that time. He belonged to "the no-hat brigade" and he was a strict tee totaller. There were no motor cars in Mesopotamia when he came so, not being a horseman, he had to do his inspections on foot. Every day he walked miles and miles visiting hospitals in the desert without proper headgear or other adequate protection against the fierce sun. Every evening he returned to the mess so exhausted as to be quite unable to eat any dinner or to digest it if he had managed to take it. We used to beg him to have a whisky and soda or other pick-me-up as soon as he arrived, but he was adamant in sticking to his teetotal rule. As everyone knows, he died from heatstroke not many weeks after his arrival in the country.

Having in mind what was said in the broadcast about what can be done under the fierce Indian sun "without injury to health," it would be interesting to learn whether during the training described there were many admissions to hospital and many invalidings attributable to "nervous breakdown," heat exhaustion, and "effects of climate."

Dr J Waterlow I was in Iraq last summer and made some measurements. One of these was of the area of the body shaded by the topee. The area shaded was about 16 per cent. in the vertical position at midday. Furthermore the protection against radiation is not complete. The shaded area is still receiving radiation from the surface of the ground, of considerable intensity. When the radiant temperature of the sun as measured by the black bulb in vacuo was 175 F., the surface temperature of the desert was nearly 160° F. Therefore the advantage given by wearing the topee is not great. My colleague Dr LADELL did some experiments showing the cooling power of a topee on a katz thermometer placed beneath it and he found that he got a slight benefit of the order of 10 or 15 per cent. with the topee.

Professor Buxton Does that mean that the protection of the topee was 10 or 15 per cent. against a hat or with no hat?

Dr Waterlow No hat at all

Dr W S S Ladell I also was in Iraq with Dr WATERLOW and would like to make a few remarks about sodium chloride and sweating. I collected sweat from twenty-four normal soldiers during the summer about five times from each man. The average sodium chloride was 0.25 per cent. which is very much the same figure as one finds in all the literature on sweating. I have not actually taken it but I think 0.25 per cent. would strike a very good mean for all the recorded figures, and that was the figure I got for my normals. It is thought that, once acclimatized, people lose less sodium chloride in their sweat. The men I collected the sweat from were all acclimatized.

ized but they were producing sweat of the same concentration as the unacclimatized. I think that shows to a certain extent that the story that people lose less sodium chloride in their sweat when acclimatized is rather misleading. I have done a certain amount of work in hot rooms and I do not believe when the evidence is sifted you will find that acclimatization leads to loss of less sodium chloride in the sweat.

Wing Commander Lee Potter. I should like to reassure Colonel JAMES that the old boggy is not entirely dead. During this war I have seen army officers wearing red lined shirts. I don't know whether they bought them as a protection against heat but presumably the tailor sold them for that purpose.

Major-General A. G. Biggam. I would like Dr. LADELL to tell us what he understands by acclimatization? What change takes place during the process we call acclimatization?

Dr. Ladell said he was not able to answer this question.

Dr. B. McArdle then put forward the view that certain changes take place during acclimatization, one of which is the earlier onset of sweating. The rectal temperature of an unacclimatized subject may rise a degree or more before he starts to sweat, whereas the same man when acclimatized will probably start sweating before his temperature had risen more than about  $0.2^{\circ}\text{F}$ . The acclimatized man also sweats more. American workers have recently shown that the energy expenditure—and the bulk of this has to be dissipated as heat—of the unacclimatized man doing a given amount of work in the heat is considerably greater than that of the acclimatized person. The effect of acclimatization on the cardiovascular system is striking and occurs mainly in the first 2 or 3 days. The body is able to provide a better blood supply to the skin resulting in a higher skin temperature, and therefore in greater evaporation and cooling than would otherwise be the case.

I have never been in the tropics but it strikes me that the umbrella is a very sensible thing. The radiant heat of the sun is a potent source of heat, and shading is an obvious remedy.

Dr. Waterlow. There are the clinical aspects of the paper. One or two things Air Commodore MORTON has not mentioned and if we could get further information about those points it would be interesting. We saw a number of cases that corresponded almost exactly to his description of heat exhaustion. Air Commodore MORTON says that the blood pressure in these cases was invariably low but I could not agree with that from what I saw and some of our cases were extremely severe. About three times out of thirty we got pressures of 80 or so but the most striking abnormality was the reduced pulse

pressure 20 instead of 40 to 50. These low pulse pressures were never seen in normal subjects. I formed the opinion that this lowering of the pulse pressure is of great diagnostic value. Otherwise it would be easy to say "This patient has a systolic pressure of 110 and is therefore all right. I noticed that some of the figures of Air Commodore MORTON's chart were of the same kind. Another point is the kind of case characterized by an abnormal skin—a dry skin and reduction of sweating but not hyperpyrexia. The rise of temperature rapidly disappears on admission to hospital, but the skin remains abnormal for a long time—2 or 3 weeks. In most of these cases there is little else wrong except complaints of weakness, dizziness and so on. The only other striking abnormality is the secretion of a large amount of urine up to about 9 litres which is greatly abnormal. We should be very much interested to know if Air Commodore MORTON found cases of this kind.

The President (Sir Harold Scott). I have very little to add before I ask Air Commodore MORTON to reply. One thing has always puzzled me. In the West Indies, we habitually wore topies during the day but would go out without hats to play tennis in the heat of the sun, or at any time of the day and in the course of a good many years there I never saw a case of sunstroke or heatstroke. Sun glare was quite common. What is the explanation? As regards the reaction of the white man and the negro to physical exertion, it is a well known fact that the black-skinned man when he starts working sweats very easily and early and in small beads, and evaporation begins earlier than with the white man doing the same work. The latter does not sweat so easily and when he does it pours off in streams. I wonder if that has anything to do with acclimatization? I was very glad indeed to hear Air Commodore MORTON's paper but what interested me equally as a pathologist, were Colonel SACHS' remarks on pathology and the details he gave I do not think are mentioned in the textbooks. I hope he will publish these findings. I think in the paper calculation in percentages on only eleven cases is apt to be misleading. The difference between a 100 per cent and 80 per cent is very little. It reminds me of a paper on anthrax which I was reading recently where the writer said it was a 100 per cent fatal in carpenters but a 100 per cent. recoveries in clergy men. I found in the author's list of cases that one carpenter got anthrax and died and one clergyman got it and survived.

Air Commodore Morton (in reply). I was glad to hear Colonel SACHS discuss the postmortems. I had three of these cases, and came to the conclusion that many of the findings we got were due to postmortem changes. The mortuary was 130 F to 140 F extraordinarily hot, and I realized very quickly that postmortem changes rapidly occurred. I sent a brain to a friend of mine, a morbid histologist, and he wrote back that he found very few changes in the brain that could not be put down to early postmortem changes but

I found widespread small petechial haemorrhages and the left ventricle was stony hard in all these cases. On the whole the changes were similar to those of Colonel SACHS but obviously on three cases one was unable to draw any hard and fast conclusions. I agree with our PRESIDENT as to the fallacy of percentages in such a small series of cases. As regards housing I agree with Professor BUXTON and I think it most important. One can nowadays for £100 buy an air-conditioned cabinet, and most of the people in the Anglo-Iranian Oil Company have got these. There is no reason at all why every hospital in the Middle East—Persia, Iraq and the hot parts of India—should not have an air-conditioned theatre. I have seen two cases die of hyperpyrexia after operation—one had been given atropine as a premedication, a dangerous thing in the hot weather, the other had not. As far back as 1930 I stressed the fact that air-conditioning in theatres was very necessary. Surgeons having to operate in hot weather are deterred very much by the risk of heat hyperpyrexia. I think in housing we should be as up to date as the Americans, and I have been most impressed with the way Americans have built their barracks out in the East, insisting on air conditioning and refrigerators. The next thing is the question of topees and I was very much interested in Colonel JAMES's remarks. I believe the khaki felt hat is perfectly all right in countries like West Africa and Burma, because there you are not dealing with extremely high temperatures but I would not like to spend a day in the sun in Iraq without a topee. During our scrapping out there we had some young army officers, and I was sent out with some of them to try and provide a water supply at a village we had captured. These boys had just come from the Western Desert and looked upon themselves as extremely tough. They wore ordinary pill box hats. I asked them, 'What about topees?' They replied, 'We did not use them in the Western Desert.' I said, 'This is not the Western Desert, this is Iraq, the shade temperature to-day is 117° F and I think you ought to borrow topees.' But they would not. I took them down in a launch. It was an open launch and on the way back I saw two of the boys looking rather funny—one said, 'I am not very well' and shortly afterwards collapsed and we spent the rest of our time pouring Euphrates water over him. If one has got an extremely good head of hair one can risk going about without a hat, but the cranium has a big blood supply and if the direct rays of the sun beat on the cranium it tends to overheat the blood generally and that is the reason for the topee. That is the advantage of the topee but spine-pads I do not think necessary. We have not used them for years but topees I would recommend for Iraq. Umbrellas I quite agree are far and away the most ideal thing but rarely practicable. Our sisters never wore topees but invariably carried umbrellas. As to foot wear I am convinced that boots, especially heavy boots, tend to push up the temperature of the body very considerably. On the 24th July 1920 during the Arab rebellion, eighty men of the Manchester Regiment were taken prisoners by the Arabs, they were stripped and



marched barefooted for many miles during the heat of the day and yet not a single case of heat effects occurred amongst them to everyone's amazement. I think the fact that they were almost naked and bare footed was a big factor in preventing heat hyperpyrexia. In the end their treatment was good and only one died in captivity. I have not seen the dry condition of the skin Dr WATERLOW has described, nor did I notice the reduced pulse pressure he records. As estimations of diastolic pressure in collapsed cases are open to fallacy we might have missed it in some cases. The question of acclimatization is of course of paramount importance in the prevention of heat effects, as Colonel DREW has stressed. Purely out of curiosity I took my temperature after three hard sets of tennis in July with an afternoon shade temperature of 110° F. It was hard exercise with the sweat pouring off me in streams, there was no rise of temperature at all either at the time or half an hour later. I was extremely surprised at this result and put it down purely to acclimatization.

## COMMUNICATIONS

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### LIZARD FILARIASIS AN EXPERIMENTAL STUDY

BY

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#### INTRODUCTION

Little is known of the stages of development of the human filarial worm *Wuchereria bancrofti* from the time of entry of the infective larvae through the skin to the fully grown forms which are met with in the deeper lymphatics in the mesentery the lymphatic glands or in the testis. During the course of an enquiry into human filariasis it was thought that a study of the life cycle of the lizard filaria might give a clue to the stages of development, since both the parasites and their embryos are similar while the insect vector the mosquito *Culex fatigans* is identical. It has also been found that the developmental stages of the parasite in the mosquito the period of maturation of the larvae the effects of environment such as temperature and humidity and the effects of hyperfilariation on the insect vector are all closely similar both for human

\* This study was supported by a grant from the Indian Research Fund Association and was part of a Filariasis Enquiry undertaken at the Andhra Medical College Vizagapatam. Our grateful thanks are due to Dr C. G. PANDIT Director and Dr K. P. MENON Assistant Director King Institute Guindy for supplying us with naturally infected lizards to start the investigation.

and lizard filariae. The lizard *Calotes versicolor* is the garden lizard of India that is sometimes called a blood sucker because of its variegated colour pattern. It is closely similar to the *Calotes marine* and is also called a chameleon from its changing tint which is most marked in the male, especially during the breeding season. Filarial infection of the lizard was first noted by CASTELLANI and WILLEY (1905) and the parasite subsequently described by VON LINSTOW (1906) under the name "*Filaria flavescens*" first suggested by their discoverers. Later PANDIT PANDIT and IYER (1929) described a similar parasite which was called "*Conspicuum gandienus*". However BAYLIS (1939) is inclined to regard both these as identical and has suggested the name "*Conspicuum flavescens*". PANDIT PANDIT and IYER (1929a) have also described the developmental stages of the parasite in the culex mosquito and showed that infection of lizards is possible experimentally by the bites of infected mosquitoes. Natural infection of lizards is found to vary very considerably in different localities. This is high in Madras while it has not so far been found in Vizagapatam in any of the seventy specimens examined.

#### MATERIAL AND METHODS.

Naturally infected lizards were obtained in hatches from the King Institute, Guindy for starting the experimental work. Laboratory bred culex mosquitoes were then infected with the lizard filaria by feeding and after the full course of development in the mosquito, the filarial larvae were collected when they had come up to the proboscis. These infective larvae were kept alive in normal saline and subsequently injected in numbers subcutaneously into healthy lizards obtained at Vizagapatam after their blood had been repeatedly examined for any natural infection. The artificially infected lizards were killed at specified intervals and the different developmental stages of the parasite obtained by dissection. From other infected lizards, tissues were obtained and fixed immediately in Bouin's fluid and Helly's fluid for histological study. For each stage of the parasite the time after injection, the site of recovery and the morphology of the parasites were all recorded and photographs of the developing forms obtained. The parasites were examined fresh and subsequently fixed and mounted in lactophenol. For histological study the tissues of infected lizards were stained by Ehrlich's haematoxylin and eosin, by Masson's trichrome stain, Maximow's azur II eosin and Leishman's stain.

#### RESULTS

##### *The Stages of Development*

1. *Infective larvae*.—These have been described by PANDIT PANDIT and IYER (1929). They measure 1,000 to 1,250 $\mu$  in length by 19 to 20 $\mu$  in width. The cuticle is smooth, the oesophagus is continuous with the intestinal canal which forms a well developed tube.

2. *Second day of development*—The cuticle is smooth, the tail and head ends are almost of the same shape, but the tail is more pointed and narrow. The head measures  $16.6\mu$  and the tail  $12.5\mu$  in width. The intestinal canal runs through the whole length, the mouth is simple without any papillae and the differentiation of the oesophagus just commencing. Anterior to the middle of the oesophagus is a constriction caused by the faint transverse striation of the rudiment of the nerve ring. The anus is subterminal without any papillae. The protoplasm is highly granular, especially in the middle of the body.

3. *Fourth day of development*—This is a small cylindrical worm with the head  $54\mu$  wide and a narrow tail end  $21\mu$  wide. The mouth is simple and the oesophagus long with a narrow anterior part and a wider posterior part separated by the faint transverse striation of the nerve ring at its middle. There are two pyriform thickenings on either side of the commencement of the oesophagus extending for about a quarter of the length of the anterior oesophagus. The intestine is tubular and uniform in diameter. At the anal opening a cloacal bulge can be made out with a cloacal papilla opening at the base of the tail which tapers from this point. Reproductive organs are not developed and the sexes not differentiated.

4. *Fifth day of development*—The worm is similar except that the posterior end of the oesophagus is constricted and beginning to be demarcated into a segment. The posterior third of the intestine is narrow and curved to one side to accommodate a thick granular mass, probably the future reproductive system.

5. *Twelfth day of development*—The general shape of the worm is similar. The oesophagus is thicker, muscular and longer, the paraoesophageal thickenings well defined and the nerve ring distinct. There are two well defined uterine tubes in the female growing from a solid column of cells in the body wall, the vaginal bud. The larger caudal tube winds round the intestine to a narrow terminal portion. The cranial tube is much narrower and tapering. Both are greenish yellow in colour. The intestine shows a well defined cloacal constriction and a terminal bulbous part consisting of a large median and a small lateral lobe. There are two well defined papillae on either side of the cloacal opening.

6. *Sixteenth day of development*—The sexes are now defined. The female worm is cylindrical, thicker and longer than the male. The body gradually narrows after the anal opening into a thumb like blunt round tip. The mouth is simple and a little below the general level. The oesophagus has a thick muscular posterior bulb with the nerve ring at the junction between the anterior fifth and the posterior four fifths. The vaginal orifice appears in the middle of the body as a thick muscular sphincter. The muscular vagina extends caudally with a dorsal convexity for  $150\mu$  and curves back to a point from which the two uterine tubes proceed and twine round the intestine as the caudal and cranial branches. The male shows a spicule like structure at the cloacal opening while the tail shows a tendency to be ventrally coiled. The coiled testicular tubules are narrow and transparent.

7 *Twenty-first day of development*—The female is by now much longer than the male. The cloacal papillae are well developed, but post anal papillae are indistinct. The intestinal canal is brown in colour and shows at the commencement an isthmus tube which is not well defined in the male. Coils of uterine tubes extend from the posterior oesophagus to the tail. The vaginal opening is well defined at about the middle of the worm. The male shows a ventral coil of the tail of about one and a half turns. The oesophagus has a short stumpy anterior part and a wide cylindrical posterior portion of about five-sixths of the length, with the nerve ring at the junction. The narrow testicular tubules encroach into the body cavity round the posterior oesophagus. The alimentary canal is brown in colour and gradually tapers down to the anus where it opens along with the vas between the cloacal papillae. The testis is long and tubular and much coiled. From its posterior end there is a short thick connecting tube which joins the vas which widens as it passes alongside the intestine to open at the cloacal aperture. The two spicules appear as one mass which is short, blunt and brownish in colour. One spicule is quite distinct while a trace of the other is embedded in the first, both lying inside the cloacal aperture. The cloacal papillae appear as one plateau on the ventral aspect of the tail with cuticular depressions on either side. The plateau is divided into a broader proximal and a smaller and narrower distal part with the cloacal opening a little behind the centre.

8 *Thirtieth day of development*—The female shows a faint transverse striation of the cuticle its tail is not tapering but rounded. It has prominent anal papillae from which there extends a transverse dorsal cuticular thickening,

#### DIAGRAM

Camera lucida drawings of the developmental forms of the lizard filaria,

*Camptocyon granulosus*

FIG 1 Infective larvae

FIG 2 4th day form note the central granular mass.

FIG 3 5th day form oesophageal junction and granular mass more marked

FIG 4 12th day form oesophageal demarcation and nerve ring definite

FIG 4a Tail end

FIG 4b Middle of body showing early sex differentiation genital opening and uterine tubes

FIG 5 16th day form head end with nerve ring oesophageal bulb

FIG 5a 16th day form, tail end

FIG 6 16th day form head end showing isthmus tube

FIG 6a Tail end showing spicule-like structure.

FIG 7 21st day form male, head end showing oesophageal bulb

FIG. 7a Tail end showing subequal spicules cloacal aperture, wavy vas and intestine

FIG 8 and FIG 9 Female and male 30th day

FIG 10 and FIG. 11 Female and male 45th day

FIG 11a and FIG 11b. Head end and tail end of 45th day male

FIG 10a Tail of female 45th day showing anal papillae

Figs 1-7  $\times$  Ca 64 Figs 8-9 10 11  $\times$  11 Figs 10a, 11a, 11b  $\times$  14

## DIAGRAM.

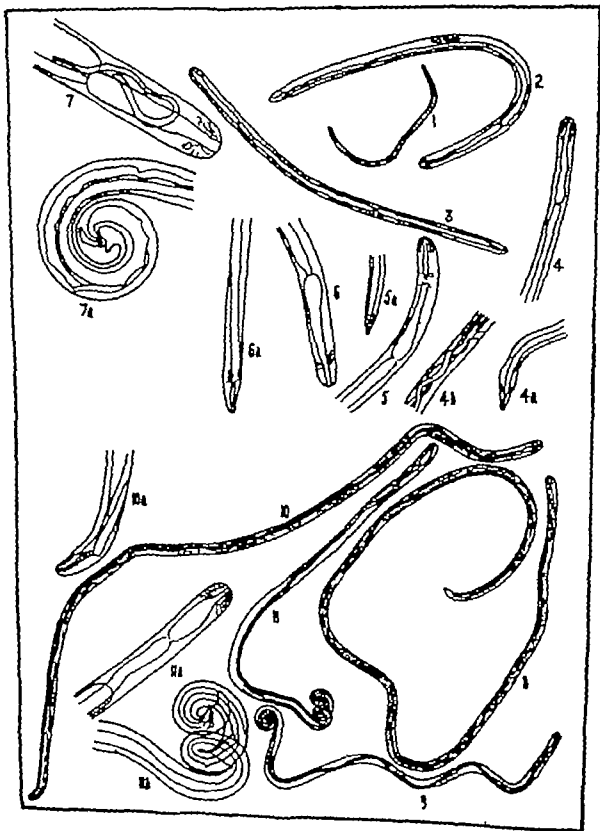
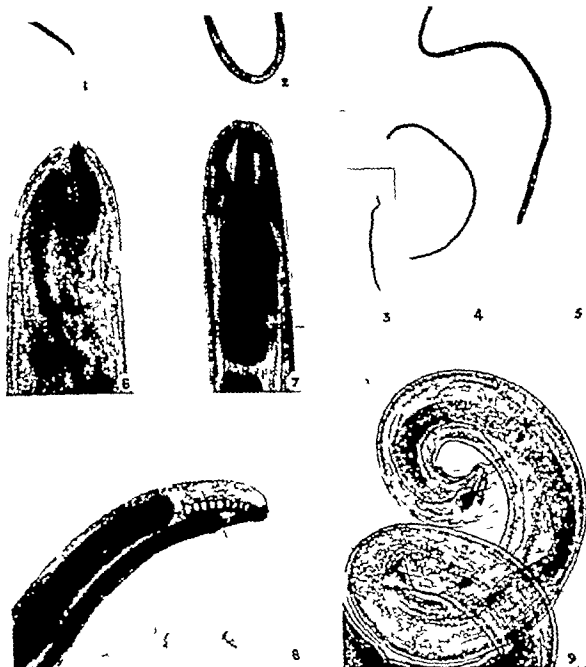


TABLE II.  
FEMALE REPRODUCTIVE ORGANS

Dev	Distance of Genital Tubercle.	Anterior limit of Uterine Tubes from Head End	Posterior Limit from Tail End	Dimensions of the Ovary	Remark.
12th	2.029 mm	1.132 mm.	1.1 mm.		Thickness of the agona, 0.034 mm. Length of the agona, 0.045 mm.
16th	4.04 mm	1.166 mm	6.173 mm		Diameter of the genital orifice including the sphincter, 29 $\mu$ . Length of the agona, 10 $\mu$ . Thickness of the vagina, 0.033 mm.
1st		0.034 mm	0.43 mm		
30th		0.8 mm	0.67 mm	16 $\mu$ 14 $\mu$	
43th	1.9 mm	4.41 mm	0.29 mm	25 $\mu$ 21 $\mu$	Five pairs of post-anal papillae. First pair 41 $\mu$ x 41 $\mu$ . Third pair 23 $\mu$ 50 $\mu$ . Last pair 25 $\mu$ 33 $\mu$ .

TABLE III.  
MALE REPRODUCTIVE ORGANS

Dev	Proximal Specula.				Distal Specula				Distal limit of Test Tube from Tail End	Anterior limit from Head End	1 thorax Tube
	Length	Width			Length	Width					
		Base	Neck	Tip		Base	Neck	Tip			
16th	The two speculae could not be made out separately. Length, 80 $\mu$ . Breadth, 30 $\mu$ .								916 $\mu$	102 $\mu$	20 $\mu$ 27.5 $\mu$
1st	They could not be well made out separately. Length of the speculae excluding cranial processes, 1.1 $\mu$ .									334 $\mu$	29 $\mu$ 80 $\mu$
		88 $\mu$	20 $\mu$	1.3 $\mu$							
30th	15 $\mu$	55 $\mu$	17 $\mu$	6 $\mu$	102 $\mu$	0 $\mu$	23 $\mu$	1 $\mu$		0.8 mm	27 $\mu$ x 46 $\mu$
43th	0.134 mm	0.036 mm	0.018 mm	0.01 mm	0.156 mm	0.089 mm	0.040 mm	0.012 mm	1.95 mm	0 mm	40 $\mu$ 50 $\mu$



# PLATE I

## DEVELOPMENTAL FORMS OF THE FILARIA IN THE LIZARD (photographs)

- FIG 1 The developing worm 24 hours after injection.  $\times 27$   
 FIG 2 The 4th day form.  $\times 27$   
 FIG 3 The 12th day form  $\times 7$   
 FIG 4 The 16th day form  $\times 7$   
 FIG 5 The male 21st day of development.  $\times 7$   
 FIG 6 The head of the female showing the oesophageal bulb and the encroaching uterine tubes 45th day of development.  $\times ca 62$   
 FIG 7 The head of the male 45th day of development  $\times 62$   
 FIG 8 The tail of the female showing the five pairs of post-anal papillae  $\times 62$   
 FIG 9 The tricoiled tail of the female 45th day of development.



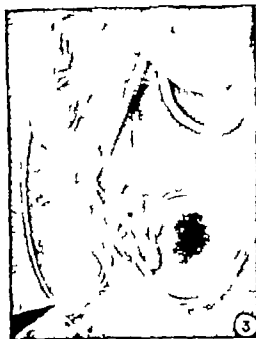


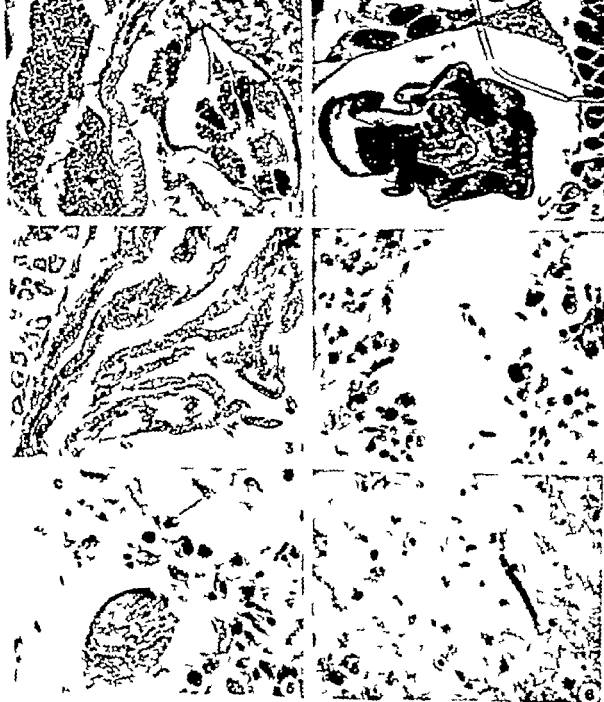
PLATE II

FIG 1 shows the oedema of the forelimb of infected bird.

FIG 2 The black arrow indicates the worm in the mesenteric

FIG 3 shows the worms lying free in the mesenteric sac  $\times 9$

FIG 4 shows the worms in the lymphatics of muscle of limb  $\times 9$



### PLATE III

- FIG 1 Female worm presumably alive in a lymphatic vessel near a vein in the limb. The uterus is filled with ova and developing microfilariae. There is little inflammatory reaction.  $\times 80$
- FIG 2 Female worm in a lymphatic vessel in muscle. Note the accumulation of macrophages at the periphery.  $\times 180$
- FIG 3 Lymphangiomatous area in the muscles of the limb near an adult worm.  $\times 80$
- FIG 4 Lymphangitis showing macrophages alongside the wall of the affected vessel.  $\times 300$
- FIG 5 Focal inflammatory changes around muscle bundles.  $\times 600$
- FIG 6 Eosinophilic coagulum with disintegrating microfilariae and leucocytes in the sheath of muscle.  $\times 600$

(Figs. 1-4 are used with permission and reuse.)



#### PLATE IV

- FIG. 1 shows the site of election of the worms in the mesenteric lymph sac.  $\times 9$   
 FIG. 2. Early stage of the encapsulating reaction round a dead worm. Inflammatory cells in surrounding coagulum.  $\times 140$   
 FIG. 3. Later stage of encapsulation.  $\times 140$   
 FIG. 4. Epithelioid cells forming the capsule around the worm.  $\times$   
 (Figs 1-4 stained with haematoxylin and eosin.)

10 *The adult worms*—These have been fully described by PANDIT and IYER (1929). The *female* is described as 95 mm. long and 0.73 mm. wide at its middle. The *male* averages 28 mm. in length and 0.3 mm. in width at its middle. Histological studies of sections of the mature worms have shown the formation of the embryos inside the uterine tubes. At first these appear as faintly eosinophilic ovoid cellular masses without any definite egg shell and appearing like segmenting blastomeres. Faint basophilic granules appear in these spherules; they become larger, the cluster of cells becomes irregularly ovoid in shape, then sausage-shaped and coiled and enclosed in a membrane. These finally become elongated to form early embryos. During this stage the basophilic granules become more prominent, increased in size and gradually arranged in the pattern met with in the microfilariae. Sections of the mature females show all the stages of development of the embryos inside the coiled uterine tubes which surround the central intestinal canal. In the *male*, the testicular tubules are on one side. They show long ovoid parallel columns of basophilic cells which become studded with very fine basophilic granules arranged in clusters like rosettes. Later these granules become coarser and lanceolate and possibly represent the homologues of the spermatids.

#### THE DEVELOPMENTAL CYCLE AND ITS SITE.

The infective larvae injected into the limbs subcutaneously migrate to the lymphatic vessels in between the muscle fibres where they increase in size. Later they migrate into the pelvic cellular tissues and from there to the mesentery. The mesentery of the lizard is a thin walled lymphatic sac without adipose tissue and lined by two layers of endothelium, one from the peritoneal reflexion and the other forming the lining of the cavity. Here they lie in between the layers of peritoneum inside the dilated lymphatic sac (Plate IV, Fig. 1). With regard to the forms of development the larvae from the mosquito show the demarcation of the oesophagus by about the 4th day while about the 12th day the genital tubercle and the uterine tubes appear in the *female*. The development of the male genital organs appears late as compared with the *female* where differentiation has been noticed on the 12th day. In 21 days the sexes are well differentiated and the spicules developed in the *male*. The alimentary canal becomes covered over by the uterine or testicular tubules. Gradually the features of adult worms appear; the colour becomes browner with age; the uterine and testicular tubes increase in size and fill up the body cavity. In the mature *female* microfilariae may be seen at the vaginal end. Microfilariae have not been met with in the heart or peripheral blood till the 41st day but have been found in the blood almost invariably in 72 days, so that the average period of maturation would appear to be about 53 days. It has further been noted that the larvae remain near the site of injection for the first 2 days. From the 4th to the 16th day they are found in the lymphatics of the muscles of the limbs. Migration, if it takes place to the mesentery, is between the 16th and 21st day. In the

mesentery or in the limbs development takes place actually inside dilated lymphatics. Infection of the mediastinal tissues may sometimes be met with by the migration of the worms, but small developmental forms are not found in the lung in any of this series. Forms recovered by dissection have shown that the activity of the worms is marked till about the 4th day they then gradually become sluggish and still later by about the 16th day activity is somewhat resumed. The site of maturation of the worms is mostly in the lymphatics of the mesentery or the retroperitoneal tissues, fairly frequently in the lymphatics of the limbs and occasionally in the peribronchial and mediastinal lymphatics. Rarely infection of the pericardium is followed by the entry of the worm into the auricular muscle.

#### THE EFFECTS ON THE LIZARD

The lizards show no discernible effects in the early stages of infection. If the infective dose is small even in the later stages with adult worms in the mesentery and microfilariae in the blood there are comparatively few noticeable changes in the lizard. Hyperfilariated lizards are dull, inactive, and do not exhibit the characteristic colour changes of the skin. They make no attempt to escape when the cages are opened, but remain stationary. There is also a disinclination for food and no active attempts are made to catch the prey. This torpor gradually increases till the animal dies. Visible oedema is not common. Only one case in this series showed increasing oedema of the fore-limb which was the one infected. This started as swelling of the antebrachium which involved the cubital fossa and gradually extended to the brachium in about 4 days. The affected limb was always kept stationary. The swelling was translucent and had extended to the distal part of the limb. The oedema was in lobular masses with intermittent ring like constrictions. During this period the blood showed microfilariae only in scanty numbers. Bacteriological examination of the fluid was inconclusive.

#### THE PATHOLOGICAL LESIONS.

Histologically it could be demonstrated that the habitat of the parent worms is the lymphatic system. In the mesentery they lie inside lymphatic vessels. In the limbs, the young forms migrate to the lymphatics of muscles and develop (Plate II Fig 4). Occasionally they lie in lymph spaces. Around the mature worms well defined changes appear in the lymphatic vessel. These undergo marked dilatation and hypertrophy with the development of plain muscle fibres in their walls as in human filariasis. Lymphatic obstruction shows itself in the formation of cavernous lymphangiomatous areas in continuation with the affected vessel (Plate III Fig 3). Polypoid projections from the wall extend into the lumen. At first these consist of vascular buds as in granulation tissue, but later they take on the characters of the vessel wall from fibrous tissue formation. While oedema is not visible to the naked eye, histologically the muscle

bundles are separated by oedematous fluid which is of muscle as well as in the loose connective tissue and inflammatory changes consist in the accumulation of cells similar to the leucocytes cells of a lymphoid type and of macrophage series. The latter accumulate inside the lymphatic vessels. The phagocytic activity to dead and degenerate microfilariae. The cytoplasm of these cells is filled with vacuoles of various sizes. Some are round and vesicular with well defined nuclear membrane. Cells resembling plasma cells are also met with. The reaction round the live worms which lie free inside the vessel appear at the periphery of the vessel. Around parasites disintegrating a series of changes is evident commencing with the formation of eosinophilic coagulating fluid which becomes infiltrated with leucocyte series macrophages, plasma cells and lymphocytes. These cells are not evident as in human filariasis. They are bound together by coarse masses of fibrin which form a thick and granular mass. Different grades of the reaction are seen when the worms are examined. Where the body of the worm is dead the inflammatory coagula appear to undergo a progressive proliferation of cells of an epithelioid type may occur (Plate IV Fig 4). Multinucleate giant cell formation is also seen with, but clusters of lymphoid nuclei at the periphery suggest symplastic fusion. These inflammatory changes are around the parent worms but around disintegrating worms on the walls of the affected lymphatic vessel. The lymphangiectasis would thus appear to be the result of the coagula. These reactions are on the whole much more pronounced around disintegrating parasites than around healthy worms. No changes are found in between the muscle fibres, but in the vascular septa separating the muscles. Here reaction to microfilariae which penetrate into the septa and are found in the tissue fibrils (Plate III Fig 6) and in the walls of the vessels. Microfilariae appear in the tissue spaces in which they have lost their sheaths and as partly digested forms as shown by the appearance of clusters of macrophages and mononuclear phagocytic cells as well as in the walls of the capillaries. The phagocytic vacuolated cells are occasional in the walls of the capillaries, but are more frequent in the walls of the lymphatic vessels. The microfilariae do not seem to penetrate the walls of the capillaries in the sheaths. Occasionally areas of lympho-vascular reactions are found around the mesentery and at the hila of the lungs.

cases unless a microscopical study of the changes involves the removal of the round dead worms and parasites and filariasis is killed only by macrophages and the products of the reaction or to disintegrate, lesions have been seen in the nodules (1942). In the lymphatic system and also well known. The part in it is possible that of these lesions of the infection in it is probably a local picture.

examined was from a ovoid cell in the uterine of periodicity of the periodic adult.

It has been worked out after infection of lizards. The site of the parasite is described. The site of the parasite suggest analogies with the parasite are demonstrated in the lymphatic system.

extensive oedema of one limb there were diffuse inflammatory changes under the skin and accumulation of oedematous fluid under the subcutaneous tissues as well as in muscle. The fluid had coagulated to form pyriform cyst-like areas. The condition suggested a secondary infection. In the *livers* of infected lizards the capillary vessels appear distended with groups of microfilariae and the capillary walls beaded. There is also a gradual increase in the supporting tissue of the alveolar walls as in chronic venous congestion. Microfilarial concentration was not met with to any extent in the *liver* and the *spleen* which showed only phagocytic activity to pigment.

### DISCUSSION

The study of the developmental forms, the period of maturation of the worm and the time of appearance of microfilariae in the blood in the lizard worms are all of interest since so far we have no accurate data with regard to the human filaria. The close similarity in the morphology of the worms, the developmental stages in the insect vector, the habitat in the lymphatic system and the pathological lesions all suggest a similar development for the human worm.

The development of the infective larvae in the deeper lymphatics and their tendency to migrate along the lymphatic vessels to the mesenteric lymphatics are features of some significance. LAXE (1937) has suggested that the infective larvae in human filariasis may enter the lymphatic system, "the lymph escalator" or alternatively the blood escalator. From the vascular system they are then supposed to enter the lymphatics of the tissues of predilection such as the testes or the retroperitoneal region. The infective larvae in human filariasis are so large (1,800–22 $\mu$ , MEXON and RAMAMURTI 1941) that a passage through the capillary system of the lung is difficult if not improbable unless they make their way through the alveolar walls into the bronchioles as do the ancylostome larvae. In lizard filariasis this experimental study has demonstrated that the lymphatic path is the one that is followed as the infective larvae (1,000 to 1,250  $\times$  19 to 20 $\mu$ , in size PANDIT *et al.* 1929) have not been demonstrated in the lung or in the peripheral blood in any of these animals. Forms met with in the hila of the lung were fully developed worms which had presumably migrated from the retroperitoneal lymphatics. In heavy infections such migrating forms could be demonstrated. The tendency for the worm to develop locally has also its parallel in human filariasis where dead or calcified worms are commonly found in the limbs in elephantiasis, while occasionally healthy worms are found in varicose lymphatic vessels or in the glands when they are dissected out.

With regard to the cause of the lymphatic obstruction that is so marked in the lizard there is very little to support a theory of abortion of the worm and discharge of ova, as such ova are much higher up in the uterus, have no distinct

egg shell and have not been found in the lymphatics in any of these cases unless there is mechanical rupture of the worm and displacement by the microtome. The evidence suggests that the obstruction is due to inflammatory changes around the worm. This reaction is not only inside the vessel but involves the vessel wall in a chronic lymphangitis. Encapsulating reactions round dead parasites and reactions with coagulum formation around disintegrating parasites have been found in the lizard. The local macrophage reaction in lizard filariasis is minimal in the neighbourhood of healthy worms that have been killed only by fixation but it is more marked around dead parasites. The macrophage reaction and chronic lymphangitis can only be looked upon as due to the products of the worm, after death, material that has escaped from the body or to disintegrating microfilariae. The part played by the microfilariae in producing lesions is also significant. Such lesions in the lymphatic system in man have been demonstrated by LANE (1933, 1934). The formation of granulomatous nodules has been described in the human spleen by DHAYAGUDE and AMIN (1942). In the lizard disintegrating fragments of the embryos surrounded by macrophages in coagula in the walls of the lymphatic vessels indicate that destruction and phagocytosis take place in the lymphatic system. Such reactions are also well marked in the sheaths of muscle and are followed by fibrous thickening. The evidence so far suggests that these reactions play a very important part in producing the obstructive lesions in lizard filariasis. It has not been possible to decide how far hypersensitization is responsible in producing any of these changes. Local necrosis of tissue due to a vascular thrombotic lesion of the Arthus type has not so far been met with. The role of secondary infections in exaggerating the obstruction and producing marked lymph oedema is probable in one case with extensive oedema of the fore limb where the histological picture suggested a complicating secondary infection.

The condition of the uterine tubes in all the adult worms examined was identical. All the stages of development of the microfilariae from ovoid cell masses to sausage forms and sheathed coils could be made out in the uterine tubes. It may be argued that this is in keeping with the lack of periodicity of the microfilariae but this can only be settled by a study of the periodic adult worms.

#### SUMMARY

The course of development of the lizard filaria has been worked out after experimental inoculation of infective larvae into non infected lizards. The different developmental stages of the parasite are fully described. The site of development and the path of the larvae in the lymphatic system suggest analogies to human filariasis. The pathological lesions caused by the parasite are demonstrated and the mechanism of production of the lymphatic obstruction is discussed.



## REFERENCES.

- BAYLES, H. A. (1936). *Fauna of British India. Nematoda*, 2, 48. London: Taylor & Francis.
- CASTELLANI, A. & WILLEY, A. (1905). *Quart J med Sci*, 49, 383.
- DRAYACUDU, R. G. & AMIN, B. M. (1942). *Amer J Path.*, 18, 351.
- LANE, C. (1933). *Lancet*, 2, 399.
- (1934). *Trans. R. Soc. trop. Med. & Hyg.* 27, 337.
- (1937). *Ibid.* 31, 61.
- VON LIEBOW, O. (1906). *Folia Zool.*, 2, 172.
- MENON, T. B. & RAMAMURTHI, B. (1941). *Indian J. med Res.* 29, 363.
- PANDIT, C. G., PANDIT, S. R. & IYER, P. V. S. (1929). *Ibid.* 16, 254.
- (1929a). *Ibid.* 17, 421.

## PORTAL CIRRHOSIS IN IRAQ

BY

R. S. STACEY M.D.

*From the Royal College of Medicine Baghdad, Iraq*

Cirrhosis of the liver is a common disease in Iraq the admissions excluding readmissions to the Royal Hospital in Baghdad being roughly one half of those for lobar pneumonia. It is found in infants, children and adults of all ages. In the following only cases occurring in persons over 14 years of age will be considered because in children the disease differs in certain respects and because the circumstances under which the cases were collected preclude, for statistical reasons, the inclusion of the younger age groups. From 136 personally investigated cases of portal cirrhosis nine have been excluded since they present differences which necessitate their separate consideration. The remaining cases show marked uniformity with respect to course symptomatology and clinical and laboratory findings. For lack of better terms the larger group will be referred to as atrophic portal cirrhosis and the smaller since the liver was in all cases considerably enlarged, hypertrophic portal cirrhosis. This latter term is not meant to imply any relationship with any other disease to which this name has been applied.

### ATROPHIC PORTAL CIRRHOSIS

This is a disease of the poorest classes and is largely though not exclusively found among persons working on the land. Out of ninety three cases, sixty five were fellahen (70 per cent.) The remainder were small shopkeepers labourers, brickmakers mudworkers, pedlars of a social standing barely above the fellahen and in only two cases could the patients be said to be moderately well to-do.

Patients from all parts and of all races in Iraq are represented, but on the basis of figures from this hospital no definite conclusion as to local incidence can be given. It is most striking that few patients came from large towns.

(d) *Syphilis plays some part in the causation of the disease in some of the cases*—This has been maintained frequently in the past for portal cirrhosis in other parts of the world, e.g. by STRIMERS (1916) LETVILLE (1918), and more recently by SCHUMACHER (1942).

On the evidence available here no final conclusion can be reached but if syphilis plays any part in the aetiology of the disease in Iraq it must be a subsidiary one since it does not occur in all cases and in those in which it does occur the symptoms are modified in details only.

#### Formol Reaction

One drop 40 per cent. formal was added to 0.5 ml. serum in a small test tube. Normal serum remains unchanged. When changes develop they are of two kinds: (a) the serum becomes cloudy this may increase until it is quite opaque; (b) the serum may form a jelly. These changes may progress for 24 hours but after that no further changes take place. Since the serum only becomes opaque when a firm jelly is formed and intermediate changes in opalescence are difficult to judge when the serum is lipaemic it was found that results could best be assessed on gel formation only. The serum was examined after 24 hours and three stages distinguished: (1) the serum remains liquid—negative reaction, (2) the serum is semi-solid, i.e. it cannot be poured from the tube but it is not a firm jelly—weak positive reaction, (3) the serum has formed a firm jelly—strong positive reaction.

In this series of cases the results were as follows: negative 11 per cent. weak positive, 21 per cent. and strong positive 68 per cent.

#### Serum Euglobulin

**Method.** The euglobulin was precipitated with 14 per cent. sodium sulphate and the tyrosine equivalent of the precipitated euglobulin estimated by Folin's phenol reagent (PROSSER and WARREN 1939).

0.2 ml. serum was added to 8 ml. 14 per cent. sodium sulphate in a conical centrifuge tube and allowed to stand in an incubator at 37° C. for at least 3 hours. The solution was then centrifuged till clear, the supernatant fluid poured off and the precipitate washed twice with 3 ml. portions of 14 per cent. sodium sulphate solution. The euglobulin was then dissolved in 4.5 ml. water. 0.5 ml. 5N sodium hydroxide solution added and allowed to stand in boiling water for 10 minutes. A standard was prepared in a 25 ml. cylinder containing 2 ml. standard tyrosine solution (0.2 gramme tyrosine in 1,000 ml. N/10 hydrochloric acid), 20.5 ml. water and 1 ml. 5N sodium hydroxide solution. The standard and the unknown were cooled to the same temperature in cold water and 0.3 ml. Folin's phenol reagent added to the unknown and 1.5 ml. to the standard. The volume of the unknown was made up to 6 ml. and after thorough mixing the colours were compared in a colorimeter. The calibration curve over the range of normal and pathological sera is not a straight line and a curve must be constructed by using standard solutions of different strengths from which the tyrosine equivalent of the precipitated euglobulin may be read. The figures given below represent therefore the mg. tyrosine per 100 ml. colorimetrically equivalent to the euglobulin in 100 ml. serum.

Table II records the results obtained in seventy six cases of portal cirrhosis and forty three control cases in which there was no evidence of any disease involving liver or spleen nor any condition such as severe anaemia or nephritis which might lead to a disturbance of the serum proteins. It will be seen that, whereas in the control group the euglobulin, expressed in terms of tyrosine, was below 60 in 85 per cent. of cases, it was above this value in 96 per cent. of cases of portal cirrhosis.

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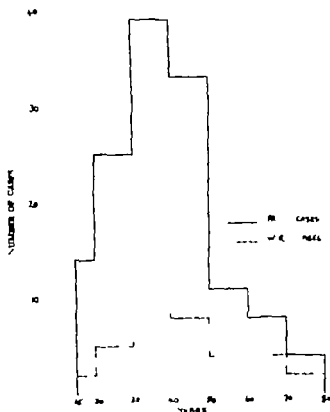
The disease is very much more common among men than women though figures would be misleading since women are less likely to present themselves at hospitals.

No instance of more than one case occurring in a family has been met with.

The majority of the cases are in the 3rd 4th and 5th decades (Graph) the maximum incidence being in the 4th. The average age was 38.2 years.

GRAPH  
AGE DISTRIBUTION OF CASES OF PORTAL CIRRHOSIS

Note—The number of cases in the age group 15 to 20 has been doubled as it is only a 5-year period



The suddenness of the decline after the age of 50 may be partly attributable to the relatively short span of life in Iraq. There is no difference in the nature of the disease in adult patients of different ages.

*Early Course of the Disease*—Treatment is rarely sought until the accumulation of ascitic fluid prevents work, so that the early stages are not often seen. The patient dates the commencement of his illness from the beginning of

abdominal distension this is usually about a month before he is first seen but varies from 10 days to 5 months. In most cases fever sometimes accompanied by chills was experienced just before the distension was noticed but no other early symptoms were reported.

*Ascites and Oedema*—Once ascites has formed, regular tapplings of the abdomen every 2 or 3 weeks are needed to avoid gross discomfort and dyspnoea and these have to be continued until shortly before death. ROLLESTON and McNEE (1929) state that tapping is seldom needed more than 2 or 3 times but most cases of cirrhosis in Iraq survive many more than this and the number may reach 40 or 50. A few cases have been met with in which ascites necessitating repeated tapping disappeared entirely enabling the patient to return to his work. After an interval in one case of two years, the ascites returned. This is probably due to the formation of a temporarily efficient collateral circulation.

Oedema usually appears first in the feet soon after the development of ascites and spreads to the thighs, scrotum, anterior abdominal wall and back but occasionally oedema precedes abdominal distension. In this series 63 per cent. of the cases were oedematous. The usual explanation of the oedema is that it is caused by compression of abdominal veins and in many cases this is confirmed by its improvement after paracentesis. That this explanation is not adequate in all cases is shown by the following—

- (a) Occasionally oedema precedes abdominal distension.
- (b) The degree of oedema does not always correspond to the abdominal tension nor is it always relieved by repeated tapping.
- (c) The oedema is often found to extend further up the back than can be explained by compression of abdominal veins and has been detected in the anterior thoracic wall.
- (d) Venous engorgement with the appearance of dilated veins forming a collateral circulation is rare.

In such cases oedema formation is due to a disturbance in the plasma proteins through liver damage leading to a lowering of the plasma osmotic pressure.

In the last stages of the disease ascites and oedema accumulate less rapidly, tapping can be postponed for longer and longer intervals and in many cases at death oedema has disappeared completely.

*Wasting*—In the early stages, wasting though present, is not marked but increases steadily until extreme emaciation is reached and the face becomes drawn and thin. The bloated face with dilated veins common in alcoholic cirrhosis is not seen.

*Liver*—This was palpable below the costal margin in the mid-clavicular line in only 7 per cent. of the cases. No evidence that a large cirrhotic liver exists at any stage of the disease was found. The average weight at autopsy was 1 063 grammes. This gives a false impression of the size of the liver as the specific gravity is above normal.

*Spleen*.—This was palpable in 65 per cent. of the cases and was always found to be enlarged at autopsy. Among a population in which malaria is endemic, much of this enlargement must be due to chronic malaria. The spleen is hard, with a well marked notch and not tender. Discomfort in its neighbourhood is often felt and many patients suffer at some time from severe attacks of pain under the left costal margin usually associated with a rise in temperature. At these times a rub can sometimes be heard or friction felt. Once the patient has come under observation a further change in size does not occur nor does the size of the spleen bear any relation to the duration of the disease or to its stage or prognosis. The average weight of the spleen at autopsy was 826 grammes and there was no relationship between the weight of the liver and spleen.

*Jaundice*.—In none of the cases was a history of jaundice given and in only 12 per cent. was there definite tinting of the sclera. This however is difficult to detect as the sclera is usually pigmented through previous conjunctivitis, medication or exposure. Fouchet's reaction on the serum was negative in 50 per cent. of the cases and strongly positive in 20 per cent. When positive, the van den Bergh reaction was a weak direct one.

*Fever*.—The course of the disease, once ascites has developed, is for the most part afebrile but many patients have short periods of fever lasting from a few days to 2 or 3 weeks. The temperature rarely rises above 38.5° C. and may be associated with pain over the spleen.

*Haemorrhage*.—Haematemesis occurred in one case only preceding by 2 weeks the development of ascites. Occasionally petechial haemorrhages are seen but there seems to be no special tendency towards epistaxis or rectal haemorrhage. The platelet count is generally reduced.

*Gastro-intestinal Symptoms*.—There is often a little epigastric discomfort but definite dyspepsia, vomiting, diarrhoea or constipation are not symptoms of the disease.

*Urine*.—This is small in volume, highly coloured, acid in reaction and precipitates urates on standing. When the abdomen is tightly distended traces of albumin are often present.

#### *Wassermann Reaction*

This was positive in 29.8 per cent. of the cases (compared with 17.8 per cent. in 500 consecutive non-cirrhotic cases admitted to the hospital). There was a history of syphilis in 3 per cent. of the cases but it is a matter of extreme difficulty to get an adequate history from the patients. In none was there any other evidence of syphilis. The symptoms, age distribution (Graph) physical signs and course of the disease were the same in the Wassermann positive and negative cases. Oedema was equally common in the two groups but splenic enlargement was slightly more common and a positive Fouchet reaction much more common, when the Wassermann reaction was positive (Table I).

TABLE I

	W.R. negative	W.R. positive.
Average age	37 years	37 years
Percentage with oedema	60	60
Percentage with splenic enlargement	61	72
Percentage with positive Fouchet	38	65

Improvement on antisyphilitic treatment (iodides mercury and bismuth) occurred in one case only though it was tried in all the Wassermann positive cases. This single case could not be observed over a long enough period to decide if the improvement was maintained. The significance of the positive Wassermann is questionable. Four possibilities present themselves —

(a) *Syphilis is coincidental* — This is unlikely as the proportion of the cases with a positive Wassermann is considerably larger than in the rest of the population.

(b) *All cases are syphilitic but a positive Wassermann is only found in some* — If this were true more evidence of syphilitic infection would have been found in previous and in family histories

(c) *A positive Wassermann does not always indicate syphilis in these cases* — Yaws and relapsing fever which may cause positive reactions, do not occur in Iraq. At one time it seemed established that malaria rarely led to a positive reaction (IYENGER 1920 JOHNSON 1921 DOWNS 1922 LLOYD and BAHADUR, 1926 SAUNDERS and TURNER, 1935) but more recent work by GREVEL, SEN GUPTA and DAS (1938) on malarial patients in India and by KITCHEN WEBB and KUPPER (1939) and BURNET MAYS and ISKRANT (1942) on inoculated malaria has led to a reversion to the opinion of early workers that a positive Wassermann reaction is likely to be met with in non-syphilitic patients during the febrile period and up to 4 weeks after its termination. In Iraq another important condition giving a positive Wassermann and caused by a *Treponema* morphologically identical with *T. pallidum* is the non venereal disease bejel. This is widely distributed throughout the country and the lesions often contracted in childhood, are unlikely to be referred to by the patient. In tuberculosis, false positive reactions occur with extreme rarity if at all, when a satisfactory technique is used (KILDUFFE, 1931 DOWNS 1922) CARDON (1942) has pointed out the association of false positive reactions with diseases in which there is hyperproteinaemia and hyperglobulinaemia. In cirrhosis of the liver hyperproteinaemia does not occur but the serum globulin is usually above normal. In twenty of the present series the globulin was estimated but the findings did not bear out the suggestion that positive Wassermann reactions could be explained in this way. From these considerations it is apparent that, on account of malaria and bejel, syphilis is less common in association with cirrhosis than the percentage of positive Wassermann reactions would suggest.



(d) *Syphilis plays some part in the causation of the disease in some of the cases*—This has been maintained frequently in the past for portal cirrhosis in other parts of the world, e.g. by SYMMERS (1916), LETULLE (1918), and more recently by SCHUMACHER (1942).

On the evidence available here no final conclusion can be reached but if *syphilis plays any part in the aetiology of the disease in Iraq it must be a subsidiary one since it does not occur in all cases and in those in which it does occur the symptoms are modified in details only*.

#### *Formol Reaction*

One drop 40 per cent formol was added to 0.5 ml. serum in a small test tube. Normal serum remains unchanged. When changes develop they are of two kinds: (a) the serum becomes cloudy; this may increase until it is quite opaque; (b) the serum may form a jelly. These changes may progress for 24 hours but after that no further changes take place. Since the serum only becomes opaque when a firm jelly is formed and intermediate changes in opalescence are difficult to judge when the serum is haemic, it was found that results could best be assessed on gel formation only. The serum was examined after 24 hours and three stages distinguished: (1) the serum remains liquid—negative reaction, (2) the serum is semi-solid, i.e. it cannot be poured from the tube but it is not a firm jelly—weak positive reaction, (3) the serum has formed a firm jelly—strong positive reaction.

In this series of cases the results were as follows: negative, 11 per cent. weak positive, 21 per cent. and strong positive, 68 per cent.

#### *Serum Euglobulin*

**Method.** The euglobulin was precipitated with 14 per cent sodium sulphate and the tyrosine equivalent of the precipitated euglobulin estimated by Folin's phenol reagent (PROSSER and WARREN 1939).

0.2 ml. serum was added to 6 ml. 14 per cent sodium sulphate in a conical centrifuge tube and allowed to stand in an incubator at 37° C. for at least 3 hours. The solution was then centrifuged till clear; the supernatant fluid poured off and the precipitate washed twice with 3 ml. portions of 14 per cent sodium sulphate solution. The euglobulin was then dissolved in 4.5 ml. water; 0.2 ml. 5% sodium hydroxide solution added and allowed to stand in boiling water for 10 minutes. A standard was prepared in a 25 ml. cylinder containing 2 ml. standard tyrosine solution (0.2 gramme tyrosine in 1000 ml. N/10 hydrochloric acid), 20.5 ml. water and 1 ml. 5N sodium hydroxide solution. The standard and the unknown were cooled to the same temperature in cold water and 0.3 ml. Folin's phenol reagent added to the unknown and 1.5 ml. to the standard. The volume of the unknown was made up to 5 ml. and after thorough mixing the colours were compared in a colorimeter. The calibration curve over the range of normal and pathological sera is not a straight line and a curve must be constructed by using standard solutions of different strengths from which the tyrosine equivalent of the precipitated euglobulin may be read. The figures given below represent therefore the mg. tyrosine per 100 ml. colorimetrically equivalent to the euglobulin in 100 ml. serum.

Table II records the results obtained in seventy six cases of portal cirrhosis and forty three control cases in which there was no evidence of any disease involving liver or spleen nor any condition such as severe anaemia or nephritis which might lead to a disturbance of the serum proteins. It will be seen that, whereas in the control group the euglobulin, expressed in terms of tyrosine, was below 60 in 95 per cent. of cases, it was above this value in 96 per cent. of cases of portal cirrhosis.

TABLE II

Serum euglobulin-tyrosine value	Normal.		Cirrhosis	
	Number of cases	Percentage	Number of cases	Percentage
0-20	10	23.2		
21-40	20	46.5		
41-60	11	25.6	3	4.0
61-80		4.7	10	13.1
81-100			10	13.1
101-120			10	13.1
121-140			11	14.5
141-160			10	13.1
161-180			12	15.8
181-200			3	4.0
201-220			5	6.6
221-240			2	2.6

The serum euglobulin is raised in other conditions *e.g.* in malaria, acute yellow atrophy, kala azar, some cases of catarrhal jaundice, amoebic hepatitis and hepatic enlargement due to cardiac failure so that the diagnostic value of the test is limited. Until further information has been accumulated as to the conditions leading to a rise in serum euglobulin, it can only be said that any case of ascites having a normal euglobulin is unlikely to be one of portal cirrhosis. The test has been found useful in differentiating such conditions as tuberculous peritonitis, abdominal carcinomatosis and hydatid disease of the peritoneum.

It has been suggested by RAY (1924), BRAHMACHARI (1923) and GANGULI (1925) that the formol reaction depends on an increase in the serum euglobulin. A comparison of the serum euglobulin and the results of the formol reaction (Table III) shows that when the euglobulin is below 60 the formol reaction is negative, above 180 it is strongly positive, while for intermediate values it may be negative, weakly positive or strongly positive. There is therefore a rough

TABLE III

	Serum euglobulin-tyrosine value			
	0-60	60-120	120-180	180-240
Formol reaction				
Negative	100	13	3%	0%
Weak positive	0	20	23%	0%
Strong positive	0%	57	74%	100%

correlation but the figures indicate that some other factor apart from the percentage of euglobulin, must be involved.

### HISTOLOGY

Numerous sections of liver and spleen examined from autopsy material showed the usual sequence of pathological changes associated with progressive atrophic portal cirrhosis and no distinctive features worthy of special note have been observed in this series of cases. Neither living nor degenerate ova of *Schistosoma haematobium* have been found in any of the sections examined and methods of digestion and concentration have likewise yielded negative results. Special attention has been directed to the detection of haemozoin as indicating a latent or past malarial infection. The presence of haemozoin in liver or spleen was a rare finding pointing to the fact that malaria plays no important part in the causation of this condition.

TABLE IV

COMPARISON OF PORTAL CIRRHOSIS IN WESTERN COUNTRIES AND IN IRAQ

	WESTERN COUNTRIES	IRAQ
Average age	A disease of late middle life Alcoholic 47.8 years. Non-alcoholic 49.8 years (ROLLISTON and McNEIL, 1929). 51.2 years (SCHUMACHER, 1937)	A disease of early middle life 36.2 years.
Sex	Male more than female.	
Heredity	Does not run in families	
Occupation	" More often seen in those whose life is sedentary than in those leading an active outdoor life (ROLLISTON and McNEIL, 1929). Rare in upper and well-to-do classes (DICKWORTH, 1874)	Principally in farm labourers  Rare in upper classes
Course of disease and appearance of patient.	Fever not common.	In general the same. Fever common.
Liver	Similar morbid anatomy and histology	
Weight of liver	1,750 grammes (ROLLISTON and McNEIL, 1929) 1,364 grammes (EVANS and GRAY 1938)	1,063 grammes.

TABLE IV—continued

	WESTERN COUNTRIES.	IRAQ
Spleen Weight of spleen	Similar morbid anatomy and histology 312 grammes (ROLLESTON and McNEIL, 1929). 526 grammes	
Jaundice	$\frac{1}{2}$ — $\frac{2}{3}$ cases (ROLLESTON and McNEIL)	12% cases but difficult to assess on account of pigmentation. Fouchet negative in 50%.
Ascites	85% cases dying of cirrhosis but more common with a comparatively small than with a large cirrhotic liver	Almost invariable
Oedema	75% cases.	63% cases.
Dyspepsia.	Common.	Not common.
Clubbing of fingers	L	Rare
Urine	Small in quantity and highly pigmented no glycosuria.	
Average duration after first tapping	46 days.	Considerably longer
Positive W.R.	Figures vary enormously CATES (1941) 10% EVANS and GRAY (1938) 12% SCHUMACHER (1937) 27% LETULLE (1918) OWEN (1921), CHAUFFORD and BRODIN (1924) 40—48% SYMERS (1916) 80%	30 cases.
Cause of death.	Progressive weakness and coma with intercurrent infection. Gastro-intestinal haemorrhage. 20% (EVANS and GRAY 1938) 31 (CATES, 1941).	Progressive weakness and coma with intercurrent infection of which bronchopneumonia is the most common. Haemorrhage is a very uncommon cause of death.

## AETIOLOGY

## Diet

Of the many factors which have been advanced as concerned in the aetiology of portal cirrhosis alcohol in western countries, is one of the most important.

In the present series all but a very few of the patients had never taken alcohol and only one had consumed it regularly. Its consumption is prevented by religion, custom and expense and it can therefore be excluded as a cause of cirrhosis in the cases considered here.

Hot spices, which have been suggested as a cause in India, are not taken to any considerable extent in Iraq. Red pepper is the only one used.

An inquiry into the diets of the class of patient among which cirrhosis is common shows it to consist mainly of carbohydrates (wheat, barley, rice and dates), vegetables and fruits. It is remarkably deficient in animal protein, meat rarely being eaten and then only in small quantities on account of expense. Avitaminoses are not common in Iraq and no particular vitamin deficiency condition has been found associated with it.

### Intestinal Parasites

The commonest intestinal parasites in Iraq are *Ankylostoma duodenale*, *Ascaris lumbricoides* and *Entamoeba histolytica*. In Table V the incidence of infestation with these parasites in the cases of portal cirrhosis is compared with that of a series of 1000 apparently healthy persons in Iraq investigated by SENKJI, BOSWELL and BEATTIE (1939).

TABLE V

	Cirrhosis	Normal
<i>Ankylostoma duodenale</i>	18%	25.6%
<i>Ascaris lumbricoides</i>	1%	13.6%
<i>Entamoeba histolytica</i>	9%	22.4%

### Malaria.

This has been said to be a cause of cirrhosis in India (SITSEN, 1923; HUGHES, 1933) and in Syria (YENIKOMSHIAN, 1934) and is endemic throughout the areas from which the patients come. A history of malaria cannot usually be distinguished from other causes of fever. None of the patients were actually suffering from malaria and it is not common to find evidence of malaria at postmortem. A number of patients were given intravenous injections of adrenaline and although this often caused a rise in temperature, it did not lead to typical malarial attacks nor to the appearance of malarial parasites in the blood.

### Bilharziasis

*S. mansoni* has been shown in Egypt by DAY (1924) to lead to cirrhosis of the liver. The form found in Iraq is *S. haematobium*, *S. mansoni* being extremely rare and only found in imported cases. In the present series there were four

cases with urinary bilharziasis. Sections of liver and spleen never revealed the presence of infection.

### *Kala-azar*

This does not occur in Iraq. Dermal leishmaniasis is common in some parts of the country but the majority of the present cases come from areas where it is not found.

*Syphilis* was discussed above and may sometimes be a contributory factor

Such a survey of the possible aetiology yields only one factor common to all cases namely poverty. This leads to a poor and restricted diet, the deficiency being principally in animal protein. Papers on portal cirrhosis in eastern countries frequently contain references to the poverty in first-class protein of the diets of those affected e.g. RADHAKRISHNA RAO (1933) and YENIKOMSHIAN (1934). ELALAN and HELFETZ (1942) have produced changes in the livers of animals kept on a protein deficient diet and MILLER and WHIPPLE (1942) have shown that such animals are particularly susceptible to liver poisons. While the literature of portal cirrhosis is full of examples of the fallacy of drawing conclusions of its aetiology from animal experiments, such experiments can be used as circumstantial evidence. It is therefore suggested that cirrhosis of the liver in Iraq is caused by a protein deficiency in the diet resulting in a liver which can be damaged by toxic substances which normally would not damage it. Malaria, syphilis and intestinal parasites are possible sources of such toxins but there are many others and different toxins probably act in different cases. Chronic alcoholism so often associated with portal cirrhosis in Europe and America, by leading to a decreased intake of food (ROMANO 1937) and by interfering with absorption may play a role in the development of cirrhosis of the liver similar to its role in alcoholic neuritis, namely by leading to a deficiency condition. This would explain the difficulty experienced by many workers in producing cirrhosis in animals by the administration of alcohol and also the similarity of the disease to portal cirrhosis in Iraq.

### SUMMARY

1. A description of the portal cirrhosis of Iraq based on 136 cases is given.
2. The condition is compared with the portal cirrhosis of western countries. The main differences are in the age incidence, the occupation of the patients, the size of the liver and spleen, the rareness of haemorrhage and the fact that alcohol plays no part in the aetiology.
3. A positive formol reaction was obtained in 89 per cent. of the cases.
4. The serum euglobulin was raised in 95 per cent. of the cases.
5. The value and limitations of the formol reaction and serum euglobulin estimation in differential diagnosis are indicated.

6. The aetiology is discussed and the conclusion reached that portal cirrhosis in Iraq is due to a dietetic protein deficiency resulting in a liver less resistant to toxins than normally. The possible sources of such toxins is indicated.

## REFERENCES

- BRAMMACHARI, L. V. (1925). *Indian med Gaz.*, 44, 295.  
 CARDON, L. & ATLAS D. H. (1942). *Arch. Derm. Syph.* 48, 713.  
 CAYE, H. B. (1941). *Arch. intern. Med.* 67, 383.  
 CHAFFORD & BRODIE (1924). *Bull. Acad. med. Paris* 81, 573.  
 DAY H. B. (1924). *Trans. R. Soc. trop. Med. Hyg.* 18, 121.  
 DOWNS, T. McK. (1927). *Amer. J. med. Sci.* 184, 514.  
 DUCKWORTH, D. (1974). *St. Bart's Hosp. med. Rep.* 10, 58.  
 ELMAN, R. & HEFFETZ, C. J. (1941). *J. exp. Med.* 73, 417.  
 EVANS, N. & GRAY P. A. (1938). *J. Amer. med. Ass.* 110, 1159.  
 FELLOWS, F. S. & PERRY W. B. (1941). *Fever Dis. Inform.*, 12, 237.  
 GANOU, P. (1925). *Indian med Gaz.* 60, 204.  
 HUGHES, T. A. (1933). *Indian J. med. Res.*, 21, 353.  
 IVINGS, K. R. K. (1929). *Ibid.* 17, 136.  
 JOHNSON, J. P. (1921). *J. Path. Bact.*, 24, 145.  
 KILGUST, R. A. (1931). *Clinical Interpretation of Blood Examinations*. Philadelphia Lea & Febiger.  
 LITTLE (1918). *Bull. Acad. med. Paris* 130, 209.  
 LLOYD R. B. & RAMAN, R. G. C. (1928). *Indian J. med. Res.*, 14, 133.  
 MILLER, L. L. & WHIFFLE, G. H. (1942). *J. exp. Med.*, 76, 421.  
 ORLINA, M. M. (1941). *Trans. Kimberley Mil. Med. Acad. Red Army*, 5, 29.  
 OWEN, L. J. (1921). *Amer. J. Syph.*, 5, 20.  
 PROSE, H. O. & WATSON, M. D. (1939). *Publ. Hlth Rep. Wash.* 54, 158.  
 RADHAKRISHNA RAO M. V. (1933). *Indian J. med. Res.* 21, 389.  
 RAY C. B. (1924). *Indian med Gaz.*, 59, 387.  
 ROLLISTON H. & McNEIL, J. W. (1929). *Diseases of the Liver Gallbladder and Bile ducts*. London Macmillan.  
 ROMANO, J. (1937). *Amer. J. med. Sci.*, 194, 645.  
 SCHUMACHER, G. A. (1937). *Ibid.* 194, 680.  
 SINGH, H. A. BOWELL, C. & BRAYNE, C. P. (1939). *Trans. R. Soc. trop. Med. Hyg.* 33, 349.  
 SITTEN A. E. (1922). *Genesee Tidjcker Med Ind* 63, 5. Abstract in *Trop. Dis. Bull.*, 20, 22.  
 STANLEY, D. (1916). *J. Amer. med. Ass.* 64, 1457.  
 YESKODONTIAN H. A. (1934). *Ibid.* 103, 660.

## LOBAR PNEUMONIA IN AFRICAN SOLDIERS

BY

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Whilst in West Africa I studied a series of cases of pneumococcal lobar pneumonia which included a type V outbreak. The patients, all African natives, were mostly recent recruits.

One assumed that natives were especially prone to succumb to lobar pneumonia (an assumption which later had to be modified) and hence they seemed ideal subjects for the evaluation of sulphapyridine therapy.

The period covered was from November 1941 to July 1942, when 159 cases of pneumococcal lobar pneumonia and 66 of atypical pneumonia\* were observed. The incidence of respiratory conditions which formed 30 to 40 per cent. of the total admissions to the Medical Division of the hospital is shown in Table I.

The sputum was examined by direct smear and if pneumococci were present in overwhelming numbers I typed them at once; if not, the sputum was plated and the predominant organism isolated. We were not able to do mouse inoculation nor any elaborate bacteriological investigation, and so cases of doubt were

\* I use the term atypical as proposed by COLE to designate all forms of pneumonia which do not conform clinically with typical lobar pneumonia. It is to be clearly understood that virus pneumonia is not referred to.



excluded. In any study of pneumonia blood cultures should be done, but this was found to be impracticable. In complicated cases, or those not responding to sulphapyridine therapy radiological examination was carried out. Nursing was done under excellent conditions by native orderlies under the supervision of a European sister. Patients remained in bed only as long as they desired. Food was abundant, of the customary native kind, and the daily intake of sodium chloride was found to be approximately 10 grammes.

TABLE I  
MONTHLY DISTRIBUTION OF RESPIRATORY CONDITIONS

	Nov	Dec	Jan	Feb	Mar	Apr	May	June
Lobar pneumonia	18	11	7	10	10	1	53	23
Atypical pneumonia	4	4	3	4	7	1	15	1
Pleurisy	0	1	0	0	1	3	14	6
Primary pleural effusion	1	0	0	0	1	1	3	2
Acute bronchitis	3	1	1	1	3	3	11	14
Chronic bronchitis	2	0	2	1	1		3	
Pulmonary tuberculosis	1	0	0	1	1	0	0	1
Arthralgia	1	0	1	0	0	0	0	0

I divided the cases into two main groups, those receiving sulphapyridine from the outset and those not so doing. Only if the cases in the latter group became sufficiently ill to make the administration of the drug imperative was it given. These three groups will be referred to as "Sulphapyridine from the onset," "Sulphapyridine delayed" and "No sulphapyridine." The gravity of the patient's condition on admission determined whether or not he received specific drug therapy at once.

#### GENERAL CONSIDERATIONS

*Reaction to pneumonia.*—Two main types of native were admitted, the so-called educated and the uneducated. The latter judged illness by four symptoms—pain, fever, headache and constipation. Cough and sputum were not often complained of and dyspnoea never. I have no doubt that the native was more susceptible to pneumonia and I was often amazed at the rapid way in which the uneducated ones recovered. When their temperature was normal they were ready to get up and return to work, even though the lung was still solid (MACNAUGHT and MURRAY LYON 1943). The educated natives on the other hand often made the plea of "I never be fit for work." I did not see any deleterious effect in allowing them to do as they pleased, although I never permitted them to return to work until fit. However on their discharge from hospital they resumed full duty.

*Mode of spread*—It was found that proximity was of no significance in the outbreak of type V pneumonia as cases arose in different places and in different camps at the same time.

*Age*—The native rarely knew his age but all were under 40 and the majority between 20 and 30 years of age.

*Diagnosis*—Lobar pneumonia was diagnosed in ninety-one cases on the day of admission in twenty three after 1 day seventeen after 2 days eighteen after 3 days, two after 4 days four after 5 days, three after 6 days and one on the 7th day

*Lobes involved*—The parts involved were right lower lobe in seventy two left lower lobe in eighty left upper lobe in six and right upper zone in thirty i.e. right lung in 102 and left lung in 86 cases. As X-rays were not always available I could not differentiate lobar involvement further

*Crisis*—The crisis occurred on an average on the 8th day of illness in the non sulphapyridine group and lysis was seen in fifteen cases.

The period of stay in hospital of these cases of lobar pneumonia was 19 to 23 days

### Complications

The complications are listed in Table II There were eight deaths three of which were directly attributable to the pneumonia

*Pericarditis*—Two cases of purulent pericarditis were seen, one a type I infection, also complicated by a lung abscess (postmortem finding) who died, and the other untyped who lived both received sulphapyridine from the onset.

TABLE II  
COMPLICATIONS.

	Malena and Silaria	Jaundice	Effusion	Empyema	Pericarditis	Meningitis	Menin- gismus	Peritonitis	Abscess	Total	Dead
Sulphapyridine from the onset	9	2	1	2	2	—	2	—	1	41	4
Sulphapyridine de- layed	1	16	4	—	—	1	—	1	—	47	1
No sulphapyridine	—	6	2	1	—	—	—	1	—	71	3

Other Complications: Herpes 1 Toxic psychosis 1 Encephalitis 1 Heart failure 1  
Partial stelectasis 2. Arthritis 4



## KALA-AZAR IN EAST AFRICA.

BY

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In a previous article (COLE *et al* 1942) a description was given of an outbreak of kala azar in a battalion of King's African Rifles. Since then other cases have been admitted to this military hospital and it is possible not only to amplify the description of the course of the disease but to give and discuss the results of treatment, and to describe the late cutaneous manifestations.

#### I GENERAL

##### A. NUMBERS OF CASES YEARS OF ADMISSION AND RESULTS

In all sixty cases have been admitted, of whom nine were not proved by finding the parasite but in whom the clinical picture corresponded exactly

My thanks are due to the DIRECTOR OF MEDICAL SERVICES East Africa Command for permission to publish this article and to Colonel WILLIAMS O.B.E. the O.C. Hospital,

They may for convenience be divided into three groups.

	Recovered		Died	Total
	Proved.	Unproved	Proved	
1 1941 cases from 2/3 KAR (described in previous article)	9	8	15	29
2 1941 other cases	4	-	4	8
3 1942 all cases	18	2	2	22

## B. PLACE OF INFECTION

Kala azar has not generally been recognized or described as occurring in British East Africa, though MAXSON BAKER (1940) mentions northern Kenya vaguely KIRK (1939) in a summary of the history and epidemiology of the disease in the Anglo-Egyptian Sudan, mentions particularly the western Abyssinian border and an area, Kapoeta, where the boundaries of Kenya Abyssinia and Uganda meet.

Of the groups of cases, those from the 2/3 KAR in 1941 were infected in the area north and west of Lake Rudolph in the neighbourhood of the Omo River. This area is near to Kapoeta, and contains sandflies in large numbers. Maximal infectivity seemed to be near the rivers, where there is moisture even in the dry season.

The other two groups however had no cases coming from this area. Some had been into southern Abyssinia as far as Mege, or even on to Addis Ababa, while others had never been north of Marsabit on the road which leads from Nairobi, via Nanyuki, Isiolo, Marsabit to Addis Ababa. Fifteen of the 1942 cases were from a Mule Transport Unit which had walked down this road from Addis Ababa to Nanyuki taking 3 months on the journey. It seems therefore, probable that there may be an endemic focus somewhere near this road south of Marsabit. This theory is confirmed by HEISEN (1942) who found fever and splenomegaly amongst the Boran tribe, and in some cases was able to demonstrate leishmaniasis. He was able to trace most of these cases to possible sources of infection on the Uaso-Nyero river which crosses the Isiolo Marsabit road at Archers Post.

## C. INCUBATION PERIOD

In the 2/3 KAR Group the incubation period could be assessed with reasonable accuracy opportunity of infection commencing 10th February and the first symptoms during June, an interval of 4 months.

A group of cases in one Company started symptoms in the second half of July and August. This Company was particularly exposed to infection in the latter half of May giving an incubation period of rather over 2 months.

This is comparable with the finding of KIRK (1939) in the Sudan who suggested 3 to 6 months.

An incubation period of 2 to 4 months was consistent with all the histories and in particular with the Mule Transport Unit. This Unit was on the road from 12.2.42 until 12.5.42 and in the suspected region in the second half of April. Cases began to present symptoms in July and August an interval of 2 to 4 months.

#### D. PERIODICITY

It is noteworthy that both in 1941 and 1942, admissions occurred in the 4 months June to September. Later cases were of long standing and had not been correctly diagnosed previously.

The possible time of infection derived either by known travel in suspected areas or by deducting the suggested period of incubation, must therefore have been March to June. This corresponds roughly with the rainy season in Northern Kenya, and is consistent with KIRK's conclusion that his maximal infectivity was from July to October the rainy season further north.

## II. SYMPTOMATOLOGY AND CLINICAL FEATURES.

### A. ONSET

This may be sudden with headache and high fever, or may be gradual with increasing fever and malaise, perhaps not reaching a maximum until the second week.

Twenty cases complained primarily of abdominal pain, seven of them with vomiting. The pain was sometimes over the spleen or liver sometimes diffusely over the upper abdomen. Five cases presented as dysentery or diarrhoea, and six others were found to have loose stools with pus or blood cells. Fourteen cases complained of pain in the chest or cough, or both two of these had a frank bronchopneumonia while the others had such physical signs as rhonchi or moist rales at one base. Three complained of pain in the neck, two with stiffness amounting to neck rigidity. Five complained of sore throat due to moderate pharyngitis.

Cases admitted late in the disease might present as debility and anaemia.

The majority with or without other symptoms gave a story of fever and malaise either sudden or gradual in onset.

### B. TEMPERATURE AND PULSE.

The only consistent feature of the fever is its irregularity and the height reached at some stage of the illness. 104° to 105° F was generally attained. Gradual rises and sudden onsets both occurred. A continuous high plateau-like course may change to a swinging remittent one. Even without therapy there is an undulant tendency dropping 1 week to 99° to 100° F and then the next week rising to 103° to 104° F. complete apyrexia for more than

24 hours was not noticed to occur spontaneously. Two or more peaks of fever in the 24 hours were frequently observed.

There is a tendency for the pulse to be faster than it should be relative to the fever especially if the fever is not severe. This is perhaps due to the carditis that occurs.

### C CLINICAL APPEARANCE

The majority of cases have been characterized by a remarkable appearance of fitness in spite of the fever. Thus, a man with a temperature of 103° F might be seen walking around the ward and making a pretty fair effort at eating his bulky food ration. On questioning he would reply as often as not, that he had no complaint of any sort beyond a certain diminution of his customary vigour or he might complain of a slight headache or abdominal discomfort.

Examination would show a clean tongue, and few physical signs beyond fever and pallor of the mucous membranes. Splenomegaly and enlarged lymph glands might also be noticed. In cases of long duration there might be severe wasting and oedema of the feet was seen even without severe anaemia.

In sharp distinction from the above four cases were admitted in a typhoidal state with dirty tongue and an apathetic manner. Also in those whose condition deteriorated, symptoms of general weakness and toxæmia would develop.

In fact while a moderate infection might be tolerated well, a more severe or overwhelming one would naturally produce a seriously ill patient.

Other clinical features are rigors, sweats, joint pains, and later some emaciation.

### D SPLENOMEGALY AND HEPATOMEGALY

Extreme enlargement of the spleen is emphasized in all descriptions. It is not invariable and, more important it is a relatively late sign. Few of these cases were admitted absolutely at the beginning of the disease and yet eleven out of the sixty did not have palpable spleens while a further twelve had spleens enlarged only 1 finger's breadth. The average enlargement of the spleen on admission was 2.1 fingers breadth. This is a degree of enlargement that might be caused by malaria in a population not completely immune.

That splenic enlargement does almost invariably occur later in the disease is shown by noting the size reached during their hospitalization. Within 6 weeks only two cases did not develop a palpable spleen, while the average maximum enlargement was 3.9 fingers breadth.

Splenic enlargement may vary rapidly and considerably. One man thought to be cured, had a spleen only palpable on deep inspiration. 2 days later in a relapse, it had expanded beyond his umbilicus. Others on successful therapy might show a reduction from six or seven fingers breadth to nothing; this reduction might be rapid—two to three fingers breadth in 4 days.

Reduction in the size of the spleen may be regarded as one of the criteria of cure. Of thirty-eight patients surviving twenty four did not have their

spleens palpable at all eight were only palpable on inspiration, and four were only one finger's breadth enlarged. One was 2F + and one 3F +. This contrasts with the findings of KIRK and SATI (1940a b c and d) where 30 per cent. remained more than 2F +.

Hepatic enlargement follows the same lines as splenic enlargement, but is slower in development and recession, is less marked, and occurs less often. Of the sixty cases, forty-four had no hepatic enlargement on admission but sixteen of these later developed some enlargement.

It must therefore be noted that while splenomegaly hepatomegaly or both, will nearly always develop sooner or later their absence in an early case does not exclude the diagnosis of kala azar.

#### E. LYMPHATIC GLANDS

Glandular enlargement occurred in exactly half i.e. thirty out of sixty cases (twenty-six of these were punctured for diagnosis). All groups of glands might be affected—cervical, axillary epitrochlear or inguinofemoral, but the latter were most marked. Enlargement was not great and the affected glands were firm and rubbery. One case was admitted as lymphadenitis. The finding of leishmania in a number of these glands indicates that enlargement is directly due to invasion by the parasites.

#### F. KIDNEYS.

Damage to the kidneys, possibly as a result of the continued fever, is of frequent occurrence. In forty cases where the urine was examined thirty-one showed albumin as a fair cloud or more, and in nineteen of these granular casts were also present. In certain cases, not immediately diagnosed and treated, albuminuria and nephritis developed as the disease progressed. In fatal cases the kidneys were swollen under the capsule, and there was damage ranging from cloudy swelling to actual necrosis and degeneration of the renal tubules. This damage appears to be an indirect toxic effect, and not due to direct parasitic invasion.

#### G. COMPLICATIONS

1. *Haemorrhage*—There appears to be an increased tendency to bleed from mucous surfaces though skin petechiae were only once seen and subconjunctival haemorrhage once. This haemorrhagic tendency is particularly associated with a severe infection, often as a terminal phenomenon. Epistaxis occurred in nine cases all severe, and twice terminally. Haemorrhage into or from the gums was seen in six cases. Haematemesis and urethral haemorrhage were seen once each. In seven cases severe bowel haemorrhage occurred terminally.

2. *Diarrhoea*—Five cases complained of dysenteric symptoms on entry and others were found to have pus or blood in the stools. Diarrhoea occurred at some stage or another in most patients illnesses and recurred frequently in those cases not doing well.



The reason for the diarrhoea and the bowel haemorrhages can be realized from postmortem examinations when the large bowel was often found severely ulcerated.

3 *Bronchitis and pneumonia*.—The frequency of bronchitis or pain in the chest as a presenting symptom has already been mentioned. Many other cases developed minor degrees of bronchitis during their illness. Two developed a definite pneumonia and recovered, in one a granulocytopenia was corrected by the infection. In three cases pneumonia was terminal.

4 *Pharyngitis sore throat dysphagia and cough with the expectoration of mucus* in twenty cases at some time during their illness. The throat appearances were indefinite the pharynx appearing granular dry or gelatinous. The condition may be associated with granulocytopenia. It seemed to be much less common in 1942 than in 1941 possibly because more effective treatment reduced the period of granulocytopenia.

5 *Anaemia*.—Secondary anaemia developed in all cases, and in some was so marked as to be the most important symptom. It was in part due to haematopoietic depression but in part to loss in epistaxis, dysentery etc. It could develop rapidly e.g. a drop of from 50 to 20 per cent Hb in less than two weeks, and took a long time to recover.

Severe anaemia, less than 30 per cent. Hb occurred in nine cases. Transfusion would of course correct the anaemia, but the need for 2,300 c.c. to raise one case from 12 to 32 per cent Hb shows that blood loss and destruction can be rapid.

6 *Oedema*.—This occurred in ten cases—usually in the feet, but three times as a general anasarca. It was connected with the anaemia, but not absolutely for some cases with severe anaemia did not develop oedema whereas other cases with moderate haemoglobin did thus, two cases with 15 per cent. or less haemoglobin had no oedema, and cases with 64 and 50 per cent showed it.

It seems probable that oedema is connected with the shift of plasma proteins from albumin to globulin, which is known to occur in this disease, and of which shift the formol gel test is an expression. No estimations, however of plasma proteins were performed. All cases with oedema had albuminuria and granular casts.

Oedema was relieved by blood transfusion, and once by plasma transfusion. It is essentially a late complication either after a long illness or where acutely ill.

7 *Dental Infections*.—It has been suggested that in kala azar or perhaps in the treatment by 4,4-diamidino stilbene, there is a tendency to pyorrhoea and dental abscess. I do not think that the records confirm this. Out of sixty cases, four needed extraction of teeth for root abscess, while one developed a necrosis of his palate and severe pyorrhoea. Only two of these five were on treatment with 4,4-diamidino stilbene. I do not think this is a higher incidence

than would occur naturally with patients making a prolonged stay in hospital, though of course the granulocytopenia present might predispose to dental infection.

There is however a symptom which has occurred in 60 per cent. of cases, and actually led to the diagnosis of cases elsewhere. This is pain in the teeth and gums without any obvious dental abnormality. Its causation is not known.

#### H. DIFFERENTIAL DIAGNOSIS

This can only indicate those diseases which most clearly simulated kala-azar or which gave most trouble, in this particular area.

Perhaps the most graphic method would be to give the various diagnoses on the Field Medical Cards or Sick Sheets with which the patients were admitted —

Malaria	24	Pulmonary T B	1
Bronchitis	6	Encephalitis	1
Influenza	3	Lymphadenitis	1
Dysentery	3	No diagnosis (including P U O	
Tonsillitis	2	N Y. D. Fever Spleno-	
Typhoid	2	megaly etc.)	17

This demonstrates what was an obvious feature — that the illness was confused with *malaria*. To complicate things further seven out of the twenty-four above had positive blood slides and practically all cases were given quinine. In fact, as a general rule absence of response to anti-malarial therapy is one of the steps in diagnosis.

The continued fever even after other signs had disappeared, demonstrated that we were not dealing with straightforward cases of *bronchitis*, *influenza*, *dysentery*, or *tonsillitis*. This would be confirmed by low polymorph count or splenomegaly or both.

*Typhoid* was excluded by the results of culture and Widal tests. *Pulm tuberculosis* presents more difficulties than might appear for the miliary produces a fever just like kala azar and definite leucopenia, and may not characteristic X-ray appearances while positive sputa are seldom found.

*Amoebic hepatitis* was also a difficulty but the higher polymorph should differentiate it speedily.

*Visceral syphilis* with enlargement of spleen and liver may simulate kala azar. The responses to anti-syphilitic treatment and the absence of prolonged pyrexia differentiate.

Finally probably the closest resemblance is borne by *undulant fever*. Sporadic cases of this disease occur in the same area. It produces a continued often irregular fever and a definite leucopenia and splenic enlargement while other incidental complications are similar to those of kala-azar. Agglutination tests or cultural isolation, if available should serve to differentiate. If not, the following clinical points may be of help: greater frequency

pains, spleen seldom greater than 2F — patient feels more sorry for himself and leucopenia and anaemia seldom so marked.

### 1 SKIN RASHES

VLANKON BARR (1940) mentions a condition "recognised by BHAKHACHARI in India and described under the name of dermal leishmanoid or post kala-azar leishmaniasis. This is a sequel to treated cases of kala azar occurring about 1 year after the disease. There is, according to him, first a stage of depigmented spots, followed by a stage of papules varying in size from a pin's head to  $\frac{1}{2}$  inch diameter. The condition may apparently last several years and ulceration may occur. Leishmania may be found in smears from the lesions.

KIRK *et al* (1938 and 1940) describe a similar condition which they differentiate from oriental sore and espundia. This is a fine punctate papular rash occurring in cases of visceral kala azar during or just after treatment. In the first article they state that leishmania are not present in the rash and speculate whether it is due to the kala-azar or to the antimony treatment. In the second they give a fuller description: the rash is first finely punctate, but later may become coarser and frankly papular; ulceration does not occur; the rash occurs during treatment after about 15 injections of stibosan and has occurred after treatment with diamidino stilbene, a non-antimonial drug; the rash commences on the face and may be confined to this area, or may spread over the trunk and rarely on the limbs; there is no itching; contrary to Indian experience, it tends to disappear spontaneously within a few months; in about 12 per cent of cases leishmania have been demonstrated in scrapings from the papules.

KIRK *et al* speculate as to whether the rash is an allergic phenomenon why it occurs only when the visceral lesions abate, and whether it has any prognostic significance.

**Incidence.**—Out of 60 cases of the series, no less than eighteen developed a definite cutaneous rash, a proportion of 30 per cent. More remarkable still is the relation of the rash to recovery: out of twenty two fatal cases only one developed the rash, thus a man who lived for 140 days and had had a full course of tartar emetic with some remission in his illness before he eventually succumbed; with thirty-eight cases who recovered, seventeen developed a rash i.e., 45 per cent.

**Drugs.**—All the rashes developed after one or more courses of therapy and at a period when there was a remission in or cure of the disease. Drugs used before the rashes developed were —

	Cases.		Cases.
Urea stibamine	6	Diamidino stilbene	3
Tartar emetic	4	Antihomaline	1
Urea stibamine and diamidino stilbene	4		

*Onset*—The rash always commenced on the face and in four cases it did not spread further. In the rest it spread on to the neck and upper trunk. In five cases it spread on to the limbs and lower trunk later. It was always most extensive and developed on the face.

In five cases the onset of the rash was associated with fever, sweating and constitutional disturbance in a patient previously afebrile. Twice this procedure was duplicated, a second disturbance heralding the appearance of the rash on the body.

*Description*—The rash always commenced as a fine miliary eruption rather like a perifollicular or sudaminal hyperkeratosis. This may last for a little and then fade or it may progress into larger papules usually fewer in number. These are acneiform and hyperkeratotic at first, but then extend and flatten into plaques exactly like a lichen. In two extreme cases warty growths formed on the nose and cheeks. Ulceration does not occur. Itching did not occur unless there was secondary infection.

*Regression*—Fading of the rash occurred in the reverse order to its appearance. Miliary punctae would disappear while the larger papules would flatten, dry and atrophy. The extreme warty growths actually fell off leaving more or less normal skin beneath. Disappearance of the rash occurred in all cases before leaving hospital in a period of from 1 to 4 months.

*Parasites*—In twelve of the eighteen rashes a scraping was examined microscopically and in eight or 66 per cent. of these leishmania were demonstrated. In two cases this was actually the way a previous clinical diagnosis was confirmed, spleen and gland punctures having failed to reveal the parasites. In three cases where multiple face scrapings were carried out, no leishmania could be demonstrated in the earliest very fine eruption but were found later when the rash grew more obvious. Parasites were generally very frequent in a fully developed rash, and there was little difficulty in demonstrating them. In all cases, the parasites disappeared from the rash and the skin before the rash itself finally went, and in no case on leaving hospital could they be demonstrated.

I think therefore, that sufficiently frequent and careful examinations would demonstrate leishmania present at some stage in the rash, and that they do not occur in the skin otherwise.

### *Conclusions*

There appears to be no doubt that the rash is associated with leishmania infection rather than with a drug. It occurs only when the patient is improving after therapy in these cases, but possibly also during natural recovery.

I think from these data a reasonable theory may be constructed. The leishmanial infection is evidently being overcome in the internal organs by the combination of drug and bodily resistance. A process then occurs somewhat analogous to the spore formation in bacteria or protozoa when conditions

become unsuitable for vegetative growth. The leishmania migrate in large numbers to the skin, causing a papular rash by their physical presence, and even causing some constitutional disturbance. Here in the skin there is a better chance of infecting an insect vector if it is thus that the disease is spread and so the race may be continued.

#### K. CUTANEOUS LEISHMANIASIS

In addition to these skin rashes in treated kala-azar one case of primary cutaneous leishmaniasis has been seen.

This man had been to Abyssinia in 1941 but had returned and during 1942 was in Nanyuki in the Kenya Highlands. He stated that in May 1942, he scratched his nose with the metal ring of a button, and that since then a warty growth developed on his nose. In July 1942, this was a flattish warty growth about  $\frac{1}{2}$  inch diameter. It was found to contain certain numerous intracellular leishmania. There was no tendency to ulceration.

It was completely obdurate to general treatment (diamidino sulbene) and to local treatment with emetine injection and tartar emetic ointment. At first it grew larger and more luxuriant, and one or two secondary warts appeared on the cheek. Leishmania remained present.

After about six months, that is about the beginning of 1943 the growth commenced to dry and atrophy in the absence of treatment. The leishmania disappeared from scrapings at about this time. By April, 1943, it has almost completely disappeared.

This lesion corresponds more closely with oriental sore than espundia, and MANKON BAH (1940) remarks on the chronicity of nasal lesions due to the former. The non-coincidence of visceral and cutaneous leishmaniasis, while emphasized by MANKON BAH is denied by KIRK and DREW (1933), who state that oriental sore, espundia, and kala-azar all occur in the Darfur Province of the Sudan.

### III. DEATHS

#### A. NUMBERS.

Fifteen out of twenty nine of the cases from the 2/3 KAR, four out of eight of the other 1941 cases, and three out of twenty three of the 1942 cases: total number of deaths twenty-two.

This was a mortality of 51 per cent in 1941 and 13 per cent in 1942, or 37 per cent. over the whole series.

All the fatal cases were confirmed by finding the leishmania but eleven, or half of these, were only confirmed in postmortem material, though spleen, liver gland or sternal smears had been examined in life in seven of them.

#### B. SURVIVAL PERIOD

Fatal cases were in hospital for an average period of 64 days before death. Times varied from 14 to 140 days. The total illness was several times not more than 20 days.

## C CAUSE OF DEATH

While of course kala azar was the primary cause, many cases died of complications of various kinds, and it is these causes or modes of death that I propose to analyze —

Dysenteric	5	Typhoidal	4
Myocardial failure	5	Asthenia	3
Pericarditis	2	Anaemia	1
Pneumonia	2		

1 *Dysentery* — Three of these had severe haemorrhage terminally and thus also occurred terminally in four of the other cases. The dysentery was persistent and refused to react to any form of treatment. Leishmania were not seen in the stools examined.

Dysenteric symptoms beforehand occurred in cases with other modes of death. Severe ulceration of the large, but not the small, bowel was found post mortem to account for the symptoms.

2 *Myocardial Failure* — There was a characteristic appearance post-mortem of a flabby heart with a gelatinous degeneration. In two cases, death occurred within 2 hours of an injection of tartar emetic, and it is probable that this drug may have contributed to some of the other deaths.

3 The cases of *pericarditis* were pneumococcal and the distinctive and fatal part of a commencing septicaemia.

4 Only two cases dying of *pneumonia* may give perhaps a wrong impression for in seven other cases some degree of bronchopneumonia was found post-mortem.

5 The *typhoidal* type of death, while of course just a product of severe toxæmia, was quite a definite entity in the 1941 cases. The patients were severely ill, with high fever and dirty tongues; they gradually deteriorated and became semi-comatose. Before death there was often diarrhoea and epistaxis.

6 The *asthenic* type did not present the same signs of toxæmia. They merely became weaker and weaker and might develop oedema or pneumonia as well as diarrhoea and epistaxis before fading out.

7 One case appeared to die of *rapidly increasing anaemia* due in part to blood loss from epistaxis and bowel haemorrhage. He died before transfusion could be arranged.

## D POSTMORTEM FINDINGS

*Heart* — Oedematous and flabby with a sort of gelatinous appearance in every case.

*Lungs* — No specific change, though often a terminal pneumonia.

*Liver* — Some enlargement and congestion was the rule. In two cases fatty degeneration of the nutmeg type was seen and in two a fine portal cirrhosis. Leishmania often present.

*Spleen*—Enlargement invariable, often very marked. Firm splenic tissue, but not excessively hard and fibrous. Leishmania often present.

*Kidneys*—All cases showed cloudy swelling of the kidney and oedema of the perinephric tissue. In three cases there was necrosis and partial disintegration of the lining of the convoluted tubules.

*Bowel*—Inflammation and mucosal damage was frequent. Marked ulceration of the large bowel was noted in four cases, and oedema of the bowel wall in two others.

*Glands*—In addition to the tendency already mentioned to lymphadenitis of external lymph glands, the mesenteric lymph glands were noted to be enlarged in four cases.

*Bone Marrow*—There was a tendency to hyperplasia. In two cases red marrow was noted in the tibiae. Leishmania always present.

*General*—Emaciation, anaemia and oedema of the tissues were frequently seen.

#### IV. HAEMATOLOGY AND LABORATORY DIAGNOSIS

##### A. RED BLOOD CELLS AND HAEMOGLOBIN

A secondary anaemia develops sooner or later in all cases. As mentioned under complications, this may be so severe as to be the most important symptom. It is probably due to a combination of causes, epistaxis and bowel or other haemorrhage on the one hand and a depression of the haemopoietic function of the marrow by toxæmia and also direct parasitic invasion on the other.

The average of blood counts on admission for all cases was 56 per cent. haemoglobin and 3,365,000 R.B.C. per c mm. the range being from 30 per cent. haemoglobin and 5,200,000 R.B.C. to 17 per cent. haemoglobin and 1,300,000 R.B.C.

If these cases were not diagnosed and treated at once, the anaemia could become rapidly more severe. Examples are 80 per cent. Hb and 4,380,000 R.B.C. on entry down to 30 per cent. Hb and 2,120,000 R.B.C. after 5 weeks. 90 per cent. Hb and 4,780,000 R.B.C. on entry down to 30 per cent. Hb and 2,180,000 R.B.C. after 6 weeks and 50 per cent. to 20 per cent. Hb in 2 weeks.

If we take the average of the lowest blood counts recorded for each patient we get the much lower figure of 37 per cent. haemoglobin and 2,520,000 R.B.C. a figure which would have been lower still if more blood counts had been done at the worst stages.

The anaemia does not react satisfactorily until the disease has been completely eradicated. Even then the response to adequate doses of iron, good diet, and a fair amount of liver by mouth, was very slow, several weeks or months being needed for more or less normal levels to be reached. This is similar to the anaemia of chronic malaria.

The average of blood counts on discharge was 72 per cent. haemoglobin and 4,165,000 R.B.C. per c mm. which though low is not far below the average

African count. Patients were not discharged until they had been at least 2 months well and symptomless.

Blood slides showed no gross abnormalities, there was some poikilocytosis and anisocytosis, the appearance probably approximates to that of TROWELL'S (1942) dimorphic anaemia.

Marrow smears were examined, more from the diagnostic than the haematological point of view and in any case require considerable experience to interpret, but no marked changes were noted except in long standing cases where the macrocytic cells containing leishmania presented a special and remarkable appearance.

#### B WHITE BLOOD CELLS AND DIFFERENTIAL COUNT

The alteration in the white blood cells is very characteristic of the disease and is of value in diagnosis. The alteration is two fold, a severe leucopenia, and an even more severe granulocytopenia with a shift in the differential count to the lymphocyte. This change appeared to occur early in the disease, without any recovery until symptoms had ceased for a long while.

The white count improves as a result of the treatment but only very slowly and even on discharge after 2 to 3 months without fever or any signs of infection still remain low. This, however may not be due to kala azar as there is a tendency in all white counts in Africans for the normal excess of granulocytes over lymphocytes and mononuclears to be lost.

##### *Average counts of 57 cases on entry*

Total W B C., 3 100 (Polymorphs 1,300 41 per cent.)

Varying from W B C. 2,200 (P 220 10 per cent.) and W B C 1 000 (P 600 60 per cent.) to W B C. 6 600 (P 2,000 30 per cent.) and W B C 5,200 (P 2,700 53 per cent.).

##### *Average counts of 37 cases on discharge*

Total W B C 4 500 (Polymorphs 2,250 50 per cent.)

Varying from W B C 2,400 (P 1,000 38 per cent.) to W B C 7 400 (P 5 600 74 per cent.)

In fact, the numbers of polymorphs on discharge were nearly double the numbers on admission.

In two cases agranulocytosis occurred. One of these died, the other was stimulated to granulocyte production by an attack of lobar pneumonia. Granulocyte production can also be stimulated by other diseases, e.g., a rise from W B C 1 400 (450 polymorphs) to 16 000 (12,000 polymorphs) after an attack of dysentery.

#### C. FINDING OF LEISHMANIA

This has meant in practice the examination of smears from punctures of living tissues and smears and sections from postmortem material.

The following tissues were examined —

Spleen smears from puncture, and postmortem material.



(WARRINGTON LORKE), a drug not containing antimony both of these for intravenous use.

#### B. CASES NOT RECEIVING ANY OF THESE FOUR DRUGS

Nine cases (seven died, all proved two lived, one proved)

- 1 Treated quinine sulphapyridine, blood transfusion, died after 38 days. Proved P.M.
- 2 Treated quinine, and anti-dysenteric measures. Died after 15 days. Proved P.M.
- 3 Treated N.A.B 5 x 0.6 gramme Tryparsamide 2 x 1.5 grammes Died after 54 days. Proved P.M.
- 4 Treated quinine, sulphapyridine. Died after 47 days. Proved P.M.
- 5 Treated tryparsamide 12 grammes Spleen puncture positive Died after 24 days.
- 6 Treated tryparsamide 12 grammes (optic neuritis) Spleen puncture positive Died after 75 days
- 7 Treated quinine Spleen puncture positive Died after 24 days.
- 8 Treated tryparsamide 11 grammes with no result. Fever subsided spontaneously later 160 days fever 66 days observation. Not proved.
- 9 Treated tryparsamide 16 grammes with no result. Fever subsided later after mumps. Sternal puncture positive 45 days fever 45 days convalescent observation.

There was little or nothing to suggest that tryparsamide exerted any effect on the course of the disease

#### C. TARTAR EMETIC

These are probably best divided into those receiving only partial courses (less than 15 grains) those receiving full (25 grains) or even multiple courses, and those receiving first tartar emetic and later other drugs

Tartar emetic was administered intravenously as for bilharzias in a strength of 1 grain in 2 cc water dosage 1 1' 2, 2, 2, 2 up to 25 grains injections alternate days

##### *Partial Courses*

- 1 Gland puncture positive Tartar emetic 15 grains No response 96 days in hospital Died 30 days after course
- 2 Liver puncture positive T.E 14½ grains No response Died during course 33 days in hospital
- 3 Postmortem positive T.E 13 grains Temperature normal 2 weeks but refused further treatment Died 83 days after course 11 days in hospital.
- 4 Spleen puncture positive T.E 7 grains Some response but died of dysentery during course 43 days in hospital.
- 5 Spleen puncture positive T.E 8½ grains No response Collapsed and died after injection 9 days in hospital
- 6 Spleen puncture positive T.E 9 grains No response Died during treatment. 22 days in hospital

7 Not proved. Clinical diagnosis only T.E. 14½ grains 12 weeks febrile before tartar emetic. 5 weeks afterwards no relapse

#### *Full Courses*

- 1 Postmortem positive T.E. 27½ grains Temporary improvement half way through course later deteriorated Died 26 days after course 62 days in hospital
- 2 Postmortem positive T.E. 27½ grains No response Died 25 days after course 97 days in hospital
- 3 Spleen puncture positive T.E. 25½ grains Temperature down 5 days Died 60 days after course 82 days in hospital.
- 4 Postmortem positive T.E. 24 grains No response Died 72 days after course 140 days in hospital.
- 5 Liver puncture positive T.E. 28 grains Temperature down 7 days Died 48 days after course 89 days in hospital
- 6 Postmortem positive T.E. 25½ grains Temperature down 7 days Died 90 days after course 131 days in hospital
- 7 Spleen puncture positive Two courses T.E. 20 and 21 grains Temperature down during first course but spleen did not shrink from 4F + to 1F + until second course Afebrile 7 months and spleen less than 1F + 2 months before discharge
- 8 Spleen puncture positive T.E. 25 grains Afebrile after five injections Spleen shrank from 4F + to nil 2½ months observation without relapse
- 9 Spleen puncture positive T.E. 22 grains Good response afebrile spleen shrank from 2F + to nil 1½ months observation without relapse
- 10 Not proved clinical diagnosis T.E. 39½ grains (two courses) Afebrile during second course 5 weeks observation without relapse
- 11 Not proved clinical diagnosis T.E. 26 grains Temperature down half way through course 1½ months observation without relapse
- 12 Not proved, clinical diagnosis T.E. 25 grains Temperature dropped towards end of course 2 months observation without relapse

#### *Cases that Relapsed and were later Treated with Other Drugs*

- 1 Liver puncture positive T.E. 21½ grains Temperature down half way through course and afebrile 1 month then relapsed. T.E. 30 grains Temperature dropped after three injections Relapse after 3 weeks T.E. 20 grains Temperature dropped towards end of course Relapse after 3 weeks At no point did the spleen shrink, but rather increased.
- 2 Skin rash positive (later) T.E. 25 grains Temperature down after five injections but rose immediately they ceased. Spleen increased.
- 3 Spleen puncture positive T.E. 28½ grains. Afebrile 3 weeks before relapse spleen remained large
- 4 Spleen puncture positive T.E. 25½ grains No complete remission. Spleen remained large
- 5 Spleen puncture positive T.E. 32 grains Remission 2 weeks then relapse
- 6 Spleen puncture positive T.E. 24½ grains Remission half way through. Relapse after 4 weeks Another remission lasting 5 weeks after pneumonia.
- 7 Gland puncture positive T.E. 35½ grains No response
- 8 Spleen puncture positive T.E. 12½ grains Afebrile for 1 month Slight fever for a week and then afebrile for 5 weeks before relapse Spleen remained large

#### *Summary and Conclusions regarding Cases treated with Tartar Emetic*

Out of twenty seven cases treated with tartar emetic, twelve died and seven recovered without other treatment, but of these latter only three had the diagnosis confirmed by discovery of the parasites In addition, remissions

varying from 5 days to 5 weeks were produced in eleven cases, and no appreciable remission in nine cases. This gives a recovery rate of 25 per cent. (all cases) or 11 per cent. (microscopically proved) under tartar emetic treatment which is not much better than the figures for No treatment at all, viz., 22½ per cent. (all cases) and 11 per cent. (microscopically proved)

However some of the cases, afterwards cured by other drugs, were presumably kept alive by the tartar emetic until other drugs became available and this value of tartar emetic is confirmed by the 55 per cent. of temporary remissions produced by its use in non successful cases

Tartar emetic is not a pleasant drug it produces cough, chest pain, and great depression just after injection, so that patients have often refused to continue with it it is easy to damage the veins with it and to produce abscesses in the arm, and it is a definite poison with an action on the heart, for one case died of sudden heart failure within an hour of injection, and others appeared to be hastened towards heart failure by it Pathological changes in the electrocardiograph during the treatment have been discussed by MAINZER and KRAUSE (1940)

Tartar emetic appears to be valuable in the treatment of kala-azar in India and Assam (MANSON BAHR 1940) but not in China or the Sudan (HARK and SATI, 1940). Experience in this series resembles the Sudan cases. Tartar emetic should never be used if other drugs are available, but in their absence it is perhaps better than nothing

## ρ ANTHIOMALINE

(A trivalent lithium salt of antimony

2 c.c ampoule contains 0.01 gramme antimony)

This drug was used in a half hearted way in 1941 giving one or two injections intramuscularly with no obvious results Two cases were successfully treated by it in 1942

1 Leishmania found in excised gland No accessible veins Treated by injections of 4 c.c anthiomaline intramuscularly on alternate days until 78 c.c were given Temperature down by slow lysis between fifth and tenth injections i.e. after 40 c.c Developed cutaneous leishmanoid rash No relapse after 7 months No untoward results of injections

2 Spleen puncture positive Had courses of tartar emetic (30 grains), diarsidino stilbene (1.15 grammes 1.01 grammes 1.13 grammes) and urea stibamine (2.15 grammes) with relapses after each Spleen had increased to 5F + but shrunk after urea stibamine to 3F + Was running fever 99 to 101 F for a fortnight when anthiomaline commenced as all veins had by now been destroyed 4 c.c was given intramuscularly on alternate days to 58 c.c Temperature normal by fifth injection Treatment ceased on account of gluteal abscess from injections No relapse after 6 months (previous longest remission 7 weeks) Spleen only palpable on respiration

These two cases suggest that anthiomaline is a useful adjunct where intravenous therapy is difficult or impossible. Large and intensive dosage is necessary such as 60 to 80 c.c. given 4 c.c. at a time on alternate days.

## I. UREA STIBAMINE.

A compound of urea with p-aminophenylstibinic acid, introduced by (and apparently manufactured by) BRAHMACHARI. He suggests two methods of dosage for adults. Standard 0.05 gramme, rising to 0.15 or 0.2 gramme intravenously in distilled water giving injections twice a week until symptoms disappear. Intensive Daily injection 0.05 rising to 0.15 gramme for 7 to 10 days, total dosage 1.5 grammes.

This drug has proved to be the most valuable we have hitherto tried, but our dosage has differed from that of BRAHMACHARI. We have used it according to three different schemes —

### (a) *Slow dosage*

(corresponding roughly with BRAHMACHARI's standard dosage)

Injections every 2 to 3 days, starting 0.05 gramme and gradually rising total 2.0 to 2.5 grammes in 15 to 25 injections in 20 to 30 days.

Eleven cases were treated by this method (all confirmed microscopically). The average time for the temperature to come down to normal was 20 days and varied between 13 and 35 days. Five cases relapsed later.

Reactions. Two cases showed a rise in temperature with the first two injections, presumably due to parasite destruction. A few complained of tightness in the chest after injection.

Evidently this dosage while it eventually brings down the temperature is not adequate, as nearly 50 per cent. of relapses occurred. This is confirmed by one case who did not even respond to the spaced injections, but responded without relapse when injections were given daily.

### (b) *Recommended Course*

(corresponding roughly to BRAHMACHARI's intensive course but more drug given)

The patient is given 14 daily injections of 0.05 0.1 0.15 0.2, 0.2, etc. Total 2.5 grammes.

Nine patients were treated by this method (seven confirmed microscopically). The average time for the temperature to come down to normal was 5 days and varied between 3 and 8 days. No relapses occurred. Four of these cases showed the reactionary rise of temperature after the first or second injection but no other ill-effects were noted.

This is the recommended treatment for all normal cases but may perhaps need modification for cases that have been mused for long periods. (See next paragraph.)

### (c) *Fatal Cases*

Three cases died when under treatment with urea stibamine. All these had been ill for a considerable period with the disease before diagnosis and in

contrast to early cases had very large numbers of parasites present. All were anaemic, and in a low state. They died, with some exacerbation of symptoms after the sixth or seventh injection (0.9 to 1.1 gramme).

It seems possible that where there are large numbers of parasites and great debility the patient's condition should be built up by transfusions until a level of 50 per cent. haemoglobin is reached and that small doses (0.15 gramme) should be used for the first week. On the other hand, equally decayed or anaemic patients did well on the recommended course and these patients might have died in any case.

#### (d) *Intensive Course*

Five cases who had relapsed after previous treatment with urea stibamine (slow dosage) diamidino stilbene tartar emetic or multiple treatments, were successfully cured with an intensive course. This idea was suggested by the improvement in results with the relatively intensive rather than slow course and the absence of unpleasant symptoms.

The dosage used was 0.1, 0.2 and 0.3 gramme daily up to 2.7 grammes in ten injections. The temperature came down in 3 to 5 days and there were no relapses. Rapid shrinkage of the spleen also took place.

#### *Summary of Cases treated with Urea Stibamine*

1. *Skin scraping positive (later)*. Relapses after temporary improvement with courses of tartar emetic (25 grains) and diamidino stilbene (970 mg.). Given 2.0 grammes of urea stibamine (rather slowly) eighteen injections in 41 days. Temperature settled after 21 days, but spleen increased from 2F + to 3F +. A papular rash developed on his face. He relapsed 1 week after completing the course temperature rising rapidly and severe epistaxis occurring. Then given diamidino stilbene (1.10 grammes, and 1.30 grammes and 1.31 grammes) in the course of the next 7 months with temporary improvements followed by relapses. Finally given an intensive course of urea stibamine (2.7 grammes in ten daily injections) temperature settled in 3 days and spleen shrank to 5F + from being well beyond the umbilicus towards the R I F. This was followed, after a month's interval, by a second similar course as the spleen was still 5F + and he had a slight fever again. Two months after this, the spleen was not palpable, he had no further relapse and his dermal leishmanoid (which had been positive) had dried up and disappeared and was negative for leishmanus. 4 months later well and fit.

2. *Spleen puncture positive*. Relapses after temporary improvements with courses of tartar emetic (grains 30), and diamidino stilbene (1.15 grammes, 1.01 grammes and 1.13 grammes). Given 2.15 grammes urea stibamine in seventeen injections over 40 days. His fever did not come down until the end of the course and he relapsed after a fortnight. Later cured with antihomaline.

3. *Gland puncture positive*. Relapses after temporary improvement with courses of tartar emetic (35½ grains) diamidino stilbene (980 mg.). Given urea stibamine 2.4 grammes in 20 injections over 45 days. Temperature did not come down until after 35 days. One month later no relapse spleen had shrunk from well below the umbilicus to 1F +. Two months later very well, no relapse.

4. *Gland puncture positive*. No response to diamidino stilbene (930 mg.). Given urea stibamine 2.05 grammes in twenty-two injections over 53 days. Temperature came down half way through course. No relapse in 6 months.

5. *Gland puncture positive*. Given urea stibamine 2.5 grammes in 14 daily injections. Very severely ill with apertaxia, bilateral optic media, anaemia (10 per cent. Hb)

needing 2½ litres of blood transfusion and also bed sores. Temperature down by end of course. Spleen shrunk to nil from 3F +. 3 weeks later developed dermal leishmanoid (positive scraping) with some fever. Was given a second intensive course of urea stibamine (2.7 grammes in nine daily injections of 0.3 gramme). Fever may have been due to large abscess in thigh. No relapse after 6 months.

6. Spleen puncture positive. Given urea stibamine 2.65 grammes fourteen daily injections. Temperature down after third injection. Spleen shrank from 1F + to nil. No relapse in 6½ months.

7. Spleen puncture positive. Diamidino stilbene 1.25 grammes relapse after 3 weeks. Intensive urea stibamine (2.7 grammes sixteen daily injections). Afebrile after 5 days. Spleen shrank from 2F + to nil. No relapse in 5½ months.

8. Spleen puncture positive. Diamidino stilbene 1.05 grammes relapse after 3 weeks. Urea stibamine 3.65 grammes spread over 42 days temperature down half way through course, and spleen down from 4F + to just palpable. 3 weeks later dermal leishmanoid (positive scraping). 5 weeks later spleen increased gradually to 3F + and a very slight evening pyrexia of less than 99 developed. Intensive urea stibamine (3.3 grammes eight daily injections) caused the spleen to shrink to nil, and also the rash to dry up and become negative. No relapse in 4 months.

9. Gland puncture positive. Urea stibamine 2.05 grammes 18 daily injections. Reactive high fever after two injections temperature down after ten. 1 week after completion of course (2 weeks afebrile) relapse. Given diamidino stilbene (1.21 grammes) response with febrile production of dermal leishmanoid, but relapse after a month. Intensive urea stibamine (2.7 grammes ten daily injections) brought temperature to normal after 4 days and spleen from 8F + to 1F + in less than 4 weeks. No relapse in 6 months.

10. Spleen puncture positive. Urea stibamine 3.05 grammes 18 injections in 29 days (daily injection last 9 days). Temperature dropped when treatment was intensified. Spleen shrank from 2F + to nil. Developed dermal leishmanoid (positive scraping) 6 weeks after course which faded and became negative in 1 month. No relapse in 8 months.

11. Skin scraping (later) positive. Urea stibamine 2.55 grammes in fourteen daily injections. Reactive peaks of fever after first three injections, temperature down to normal after six. Dermal leishmanoid developed 2 to 3 weeks after course with positive skin scraping. Rash faded and became negative in 1 month. No relapse after 7½ months.

12. Gland puncture positive. Remission and relapse with diamidino stilbene 1.25 grammes. Urea stibamine 2.15 grammes 18 injections in 43 days. Temperature normal after 20 days two febrile reactions later with appearance of dermal leishmanoid on face and then on body (skin scraping positive). Afebrile for 14 days then relapse. Steady increase of spleen from 3F + to 8F +. Intensive urea stibamine (2.7 grammes ten daily injections) temperature down in 4 days spleen to 1F + in 16 days. In 2 months rash atrophied and negative. No relapse in 6 months.

13. Spleen puncture positive. Urea stibamine 2.5 grammes in fourteen daily injections. Reactive hyperpyrexia second injection, afebrile after four. Spleen 1F + disappeared by end of course. Slight rash lasting 14 days developed 7 days after course. No relapse in 8 months.

14. Spleen puncture positive. Urea stibamine 2.5 grammes in fourteen daily injections. Reactive peak of fever after first injection. Afebrile after 5 days. Spleen 1F + to nil by end of course. No relapse in 8½ months.

15. Gland puncture positive. Urea stibamine 2.5 grammes in 14 daily injections. Reactive peak of fever after first injection. Afebrile after 5 days. Spleen 3F + to nil by end of course. No relapse in 8 months.

16. Spleen puncture positive. Urea stibamine 2.5 grammes in 14 daily injections. Initial reaction, afebrile after 3 days. Spleen 6F + to 1F + by end of course. No relapse after 8½ months.

17. Gland puncture positive. Urea stibamine 2.45 grammes in 18 daily injections. Afebrile after 14 days. Spleen 1F + to nil by end of course. Slight fever at end of course for 2 days with appearance of dermal leishmanoid which faded in 6 weeks. No relapse after 8½ months.

18. Spleen puncture positive. Urea stibamine 2.10 grammes in 17 injections in 28 days. Afebrile after 13 days. Spleen remained large 3F - by end of course but disappeared in the next 2 months. No relapse in 8 months.

19. Gland puncture positive. Urea stibamine 2.10 grammes in 14 injections in 31 days. Afebrile after 14 days. Spleen 3F + to nil. No relapse in 10 months.

20. Not proved microscopically. Urea stibamine 2.5 grammes in 14 daily injections. Afebrile after 3 days. Spleen 4F + to nil. No relapse in 6 months.

21. Not proved microscopically. Urea stibamine 2.6 grammes in twelve daily injections. Before treatment epistaxis, fever, anaemia 17 per cent necessitating transfusion. Spleen 6F +. Temperature down in 8 days. Spleen 1F + at end of course. 1 month later Hb 60 per cent. and spleen not palpable. No relapse in 6 months.

22. Postmortem positive. Died of dysentery after 1.10 grammes urea stibamine. Very large number of leishmania.

23. Gland puncture positive. 6 months undiagnosed. Anaemia and general oedema, Hb 40 per cent., two blood transfusions and 1.70 grammes urea stibamine. Died of pneumonia. Very large number of leishmania.

24. Spleen puncture positive. Urea stibamine 0.9 gramme. haemoglobin dropped quickly to 15 per cent. Died partly of anaemia before transfusion could be given. Large number of leishmania.

#### F 4-4-DIAMIDINO STILBENE OR M & B. 44

This drug was introduced by Prof WARRINGTON LOURIE (LOURIE and YORKER, 1939) and found to be trypanocidal and also of value in Indian kala azar (ADAMS and YORKER 1939). KIRK and SATI (1940) reported favourably on it in Sudan kala azar. They obtained immediate improvement in twenty-four out of twenty-eight cases, but were only able to follow up four cases for 4 months: these did not relapse. Their total dosage varied from 750 mg to 4.9 grammes, and they were trending towards a relatively intensive course of 100 mg daily for 15 days, followed by a similar course after a week's interval: total dosage, 3 grammes, or about 60 mg per kg. They do not specifically mention relapses, but recount exacerbations of fever on commencing new courses. Amongst complications they had syncopal attacks with coma (twice) and also breathlessness, giddiness, and vomiting.

The drug is not very soluble but 10 mg can be dissolved in 1 c.c. of distilled water. It is given intravenously.

**Results.**—Fourteen cases were treated with this drug. No absolutely definite scheme of dosage was used but about 1 to 1.3 grammes in twelve injections spread over 14 to 30 days. Of the fourteen cases seven were cured (three of these had had previous tartar emetic treatment) one of these relapsing once and needing a second course. Courses of treatment in successful cases varied between 1.07 grammes in twelve days and 1.18 grammes in 29 days to the only intensive course used, 2.5 grammes in 14 days.

In the seven cases not cured, several courses were tried on some and there were in all eleven relapses and twice no response to the drug. Response to diamidino stilbene is slower than to urea stibamine, the temperature becoming normal between 2 and 32 days after starting treatment, with an average of 12½ days.

The relatively unsuccessful results with this drug are due to inadequate dosage and inadequate intensity of treatment for this are mechanical, in that diamidino stilbene is not in 10 c.c. and that suitable syringes holding more than 10 c.c. to obtain medical in that the drug has some unpleasant side effects set out in detail in the next paragraph. The only case treated on a course of 50 mg 100 mg 150 mg and 200 mg daily to 2.5 g without relapse and it is hoped to try this type of course if epidemic occurs.

**Toxicity**—Unpleasant sensations of tightness in the chest or through the veins or of great depression occurred in about 10 cases. Vomiting only occurred once. It has already been mentioned that the drug was suspected probably without justification of causing collapse. In one case collapse occurred which was found on careful examination due to an extreme drop in blood pressure (110/75 to 60/40), a very slow pulse, and relieved by adrenaline. Use of the drug had to be stopped.

These do not sound very serious but contrasted with the appearance of urea stibamine they do not encourage use of the drug in patients.

#### *Summary of Cases treated by Diamidino Stilbene*

- 1 Skin scraping positive (later) Relapse after tartar emetic.
  - (a) Diamidino stilbene 970 mg in sixteen daily injections. No reactions. Spleen unaltered. Relapsed 16 days after course urea stibamine.
  - (b) Diamidino stilbene 110 grammes in twelve injections. Reaction at first with expansion of spleen. Temperature down 2° C. shrank from 6F - to 1F + by end of course. Relapsed 45 days up to 5F -.
  - (c) Diamidino stilbene 130 grammes in thirteen injections. Temperature down in 4 days. Spleen 4F +. Relapsed 43 days after course.
  - (d) Diamidino stilbene 131 grammes in fourteen injections. Intermittent fever through and after course. Spleen enlarged umbilicus. Later cured by intensive urea-stibamine.
- 2 Spleen puncture positive. Relapse after tartar emetic.
  - (a) Diamidino stilbene 680 mg in twelve injections in oedema and spleen beyond umbilicus (7F +). Temperature spleen 5F -. Relapse after 5 days so treatment recommenced.
  - (b) Diamidino stilbene 117 grammes in thirteen injections. Temperature normal in 9 days. Spleen very painful at first, down to 3F. Oedema of feet also disappeared. Dermal leishmaniasis (by course) 4 months later the skin rash after developing and dropping off spleen still 3F + no relapse.
- 3 Spleen puncture positive. Relapse after tartar emetic.
  - (a) Diamidino stilbene 120 grammes in thirteen daily injections. Temperature shrank from 8F + to 5F + oedema of the feet disappeared.
- 11 No relapse in 3 months.
- 4 Spleen puncture positive. Relapse after tartar emetic.
  - (a) Diamidino stilbene 990 mg. in fifteen daily injections in 30 days. Spleen 6F down to 3F by end of course. Spleen enormous 8F +.



(b) Diamidino stilbene 1.14 grammes in twelve injections in 23 days. Temperature down in 7 days. Spleen 2F — 1 month after course. No relapse in 3 months. Spleen puncture positive. Relapse after tartar emetic, 30 grains.

(a) Diamidino stilbene 1.15 grammes in 19 injections. Afebrile in 12 days. Relapse after 32 days.

(b) Diamidino stilbene 1.41 grammes twelve injections in 22 days. Febrile reaction and enlargement of spleen at first. Afebrile 10 days. Spleen shrank from 7F — to 1F — 10 days after course. Relapse after 73 days. Fever and spleen 8F +.

(c) Diamidino stilbene 1.13 grammes 13 injections in 23 days. Afebrile 18 days. Relapse after 52 days.

Later cured with urea stibamine and antithromaline.

6 Gland puncture positive. No response to tartar emetic 351 grains. Diamidino stilbene 600 mg. sixteen daily injections. Afebrile by end of course. Relapse after 20 days.

Later cured by urea stibamine.

Spleen puncture positive. Relapse after response to tartar emetic 1 grain. Very slight fever only, but not fit and spleen 6F —. Diamidino stilbene 1.19 grammes twelve injections in 29 days. No fever after 2 days. Spleen 7F — only by end of course. No relapse in 3 months.

8 Liver puncture positive. Partial responses with three courses of tartar emetic 4 months low irregular fever since last course. Spleen 4F —.

Diamidino stilbene 1.07 grammes twelve daily injections. Afebrile after 4 days. Spleen disappeared 1 month later.

No relapse in 2½ months.

9 Gland puncture positive. Diamidino stilbene 800 mg. twelve daily injections. No response. Cured with urea stibamine.

10 Gland puncture positive. Spleen 3F —. Diamidino stilbene 2.5 grammes in 14 daily injections. Temperature down in 14 days. Developed palatal necrosis, which healed 3 months later well and fit. Spleen not palpable. No relapse in 6 months.

11 Spleen puncture positive. Diamidino stilbene 1.03 grammes in twelve daily injections. Temperature down in 8 days. Relapse after 70 days. Cured with urea stibamine.

12 Spleen puncture positive. Diamidino stilbene 1.23 grammes fourteen injections in 29 days. Temperature down in 18 days. Relapse in 21 to 23 days. Cured with urea stibamine.

13 Gland puncture positive. Diamidino stilbene 1.25 grammes in sixteen daily injections. Temperature down in 4 days. Relapse after 22 days. Cured with urea stibamine.

14 Gland puncture positive. Diamidino stilbene 1.25 grammes in fourteen daily injections. Temperature down in 4 days. No relapse in 9 months.

### C. ADDITIONAL THERAPY

While in all cases symptomatic therapy and the treatment of such complications as bronchitis and dysentery is necessary there are some additional procedures that are almost specific, and others that are valuable. The most important is *blood transfusion*. I have mentioned that secondary anaemia is common, that in severe cases oedema occurs and that epistaxes and other mucous bleedings are frequent complications. The best and, in fact, almost the only treatment for these consists in transfusion. While small transfusions (1 pint) are a help the good effects may be rapidly lost, and as a counsel of perfection I would recommend continuous drip transfusion till a figure of at least 50 per cent. haemoglobin is reached. Specific therapy (*e.g.* urea stibamine) can be added to the drip.

There is reason to believe that blood transfusion has a good effect on the severe dysentery that may occur in kala-azar (comparable with the effect in ulcerative colitis)

The only evil effects of transfusion are first, the strain on the heart, which is avoided by a slow drip and lessened by the improved nutrition resulting second the tendency to pulmonary congestion and pneumonia this has to be risked and infection treated with sulphapyridine.

*Diet*—These patients eat well but burn their tissues rapidly and every opportunity should be taken to improve their wasted condition with meat, and diet rich in all vitamins.

*Iron Therapy*—This appears to be logical though the response is not dramatic. The marrow needs every aid in its task, made difficult by infection.

*Liver Therapy*—Probably best tackled by adding raw and lightly cooked liver to the diet. Injections of liver extract do not produce any marked result.

## VI RELAPSES AND CRITERIA OF CURE.

### A RELAPSES

It will have been noted that relapses after apparent cure have been a frequent occurrence perhaps due to inadequate therapy. This unfortunate tendency makes it more difficult to know when in fact, a patient is finally cured. Amongst the sixty cases, or rather amongst the thirty-eight who recovered there were thirty-one relapses after temporary cure in eighteen patients. The period between the end of the course of treatment and the apparent relapse varied between 7 and 73 days with an average of 25 days  $2\frac{1}{2}$  months therefore, appears to be the minimum period of observation necessary before pronouncing a cure, and 3 months more desirable. No relapses occurred in patients who had gone longer than 21 months safely even though observed from 6 to 9 months.

It might be interesting to give a summary of one of the cases showing the most frequent relapses

#### CASE.

Pain in left hypochondrium and fever 8 days Spleen 3F + Spleen puncture positive W.B.C. 3,000  
 28.8.41 to 14.10.41 Tartar emetic grains 24 1.10.41 afebrile  
 23.10.41 Fever recommenced, spleen 4F + W.B.C. 2,800  
 27.10.41 to 14.11.41 Tartar emetic grains  $5\frac{1}{2}$   
 19.11.41 Incomplete response W.B.C. 4,200 spleen 4F +  
 1.12.41 to 18.12.41 Diamidino stilbene 1.15 grammes 12.12.41 afebrile  
 22.12.41 Spleen 3F +  
 24.12.41 Sent out on sick leave but returned 29.12.41 for administrative reasons  
 W.B.C. 1,200  
 13.1.2 Fever recommenced up to 102 to 103° F Spleen enlarged to 6F +  
 21.1.42 to 22.2.42 Diamidino stilbene 1.01 grammes  
 16.2.42 Developed pneumonia

- 20.2.42. Afebrile spleen 1F + only  
 24.3.42. W.B.C. 3,200  
 14.4.42. No fever for 53 days Sent to convalescent camp.  
 24.4.42. Readmitted with fever 101 to 102 F and spleen below umbilicus "F +"  
 30.4.42 to 23.5.42 Diamidino stilbene 1.13 grammes Arytzeal 16.8.42.  
 6.6.42 Spleen 3F + Liver 2F + W.B.C. 8,500  
 6.7.42. Relapse spleen 6F -  
 20.7.42 to 23.9.42 Urea anhydrous " 15 grammes 18.9.42 apyretical, dermal leishmanoid  
 2.10.42 Low fever again.  
 15.10.42 to 9.11.42. Anthiomalme 50 c.c. 25.10.4 afebrile 1.11.42 spleen 2F -  
 11.1.43 spleen 1F - W.B.C. 5,900.  
 20.4.43 Spleen not palpable Well and fit 6 months without relapse

## B. CRITERIA OF CURE

*Fever*—This is the most obvious and important No stretch of the imagination could say that a patient was cured until his fever ceased. But the paragraph on relapses shows that a minimum afebrile period, after ceasing treatment, of 2 to 3 months is necessary before cure can be assumed.

*General Condition*—This is of considerable value If a patient gains weight rapidly and looks well and feels well, he is less likely to relapse than one who in spite of apparent cure "hangs fire"

*Spleen*—Unless there is a definite reduction in size of the spleen during the course, followed by progressive diminution afterwards if still palpable, relapse may be confidently expected As already mentioned only two cases showed enlargement more than 1F - on discharge

*Blood Count*—While the white blood count improves with treatment, study of the figures given in an earlier section shows that this is not sudden and dramatic. The white count unless taken under similar conditions each time varies irregularly and in Africa never reaches the figures regarded as standard for Europeans. An improved white count is, therefore merely a confirmation that the case has improved. Curiously enough the haemoglobin and R.B.C. are of more value in following the prognosis of the case If these do not rise to adequate figures (70 per cent. Hb and 4,000,000 R.B.C.) it is possible that the infection is latent and a relapse is possible.

*Parasites*—Disappearance of the parasites from the tissues is a necessary condition to be satisfied before cure is pronounced. But in most early cases parasites are scanty and difficult to find anyhow and soon disappear on treatment When dermal leishmanoids appear it is necessary to ensure that skin scrapings are negative before discharge for the parasites appear to persist here longer than elsewhere

## SUMMARY

As criteria of cure there must have been no fever for 3 months the patient must be well and fit and have gained weight, his spleen must have shrunk to not more than 1F - and his blood count have improved, while parasites should not be demonstrable anywhere

## VII SUMMARY

An account is given of 60 cases of kala azar admitted to a military hospital in East Africa. The epidemiology, clinical features, complications, and post mortem findings are described. The treatment and criteria of cure are discussed, and the success of urea stibamine in adequate dosage is emphasized.

## VIII REFERENCES

- ADAMS A. R. D. & YORKE, W. (1939) *Ann trop Med Parasit.* 33, 323.  
 BRAHMACHARI, U. quoted by MANSON BAHR.  
 COLLE, A. C. E., COSGROVE, P. C. & ROBINSON, G. (1942) *Trans R. Soc trop Med Hyg.*, 36, 25.  
 HEISCH, R. (1942) *Personal Communication*.  
 KIRK, R. (1939) *Trans R. Soc trop Med. Hyg.* 32, 533.  
 ——— & DREW, C. B. (1938) *Ibid.* 32, 265.  
 ——— & SATT, M. H. (1940a) *Ibid.* 33, 501.  
 ——— ——— (1940b) *Ibid.* 34, 213.  
 ——— ——— (1940c) *Ann trop Med Parasit.* 34, 83.  
 ——— ——— (1940d) *Ibid.* 34, 181.  
 LOURIE, E. M. & YORKE, W. (1939) *Ibid.* 33, 289.  
 MAINZER, F. & KRAUSE, M. (1940) *Trans R. Soc trop Med Hyg.* 33, 405.  
 MANSON BAHR, P. (1940) *Manson's Tropical Diseases* p. 174. 11th ed. London: Cassell & Co.  
 TROWELL, H. C. (1942) *Trans R. Soc trop Med Hyg.* 36, 151.



## CUTANEOUS LEISHMANIASIS IN NIGERIA

BY

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AND

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Nigeria is included in the geographical distribution of cutaneous leishmaniasis by CRAIG and FAUST (1937) and MANSON BAHR (1940) but for many years there has been considerable local doubt as to its existence.

SMITH (1932) mentions that positive findings have been reported occasionally in Northern Nigeria though in a later publication (1939) he states that the disease has not yet been proved to occur in Nigeria. On the other hand McCULLOCH (1928) asserts that cutaneous leishmaniasis is definitely established in Northern Nigeria and that sections are the only safe method of diagnosis. It is to be regretted that he does not mention the number of cases proved by finding the parasite as this is the only reference we have been able to find confirming its occurrence in this country.

The *Annual Reports of the Medical and Health Services of Nigeria* for the years 1924 to 1941 record 131 cases of cutaneous leishmaniasis and five cases

\* The authors are indebted to the DIRECTOR OF MEDICAL SERVICES, Nigeria, for permission to publish and to Mr J. E. KNIGHT, Laboratory Superintendent, for the photographs.

of kala-azar but there is no mention of positive laboratory findings during this period and it is safe to assume that in the majority the diagnosis was solely on clinical grounds.

MCCULLOCH (1930) was in charge of the pathological laboratory at Kaduna, Northern Nigeria, during 1929 but his report contains no reference to cutaneous leishmaniasis, nor do those of his predecessors and successors. This laboratory served the whole of the Northern Provinces for many years.

One of us (R. N. H.) had observed clinically suspicious cases at Sokoto Northern Nigeria, in 1930 but was unable to confirm the diagnosis microscopically. Further attempts over a number of years at Kano were also unsuccessful but in 1942 leishmania were found in smears from a cutaneous sore by the African Technical Assistant at the City Hospital, Mr S. ENO. Fourteen cases were diagnosed microscopically during that year but the record of them was unfortunately lost and it was decided to send smears from subsequent cases to the Medical Research Institute for confirmation. This was done and up to the time of writing ten confirmed cases have been seen at Kano during 1943.

#### Cases.

Case 1.—A European male on leave from Maradi in French Niger Colony reported with multiple ulcers on one leg which he said had commenced as small boils a month previously.

Case 2.—A European male also from Maradi, had multiple papules on his arms and legs of 1 month's duration.

Case 3.—An African male a native of Southern Nigeria but living in Kano had typical lesions on the thigh with a 4 weeks' history.

Case 4.—A Tripolitanian Arab male living in Kano who had papules and ulcers on both legs.

Case 5.—A European male from Zaria in Northern Nigeria where he might have become infected. He had indolent ulcers on the legs of 3 months' duration.

Case 6.—An African female from Sokoto Northern Nigeria, who had been in Kano for a year. She had extensive ulceration of the right breast and numerous fusiform bacilli were found in the smears as well as leishmania. The case was probably tropical sloughing phagedaema superimposed on cutaneous leishmaniasis. The disease was stated to be of 6 months' duration.

Cases 7, 8 and 9.—African males, natives of Kano who had single lesions on the arm.

Case 10.—An African male native of Kano with an indolent ulcer of the leg.

In all the cases the lesions conformed with the textbook description of oriental sore and they responded well to treatment with tartar emetic. The parasites found in smears stained by Leishman's stain were typical of *Leishmania tropica* and exhibited the range in size and shape associated with this species. A seasonal incidence, towards the end of the rains, has been noted. The species of sandfly occurring in this area of Nigeria have not yet been identified. Kano is situated about 12° N. 8.5° E. and Maradi lies some 150 miles to the north west. The French Medical Officer there, Dr D. VAREZ, in a personal communication, states that cutaneous leishmaniasis is not uncommon in his district. In Southern Nigeria, whose geographical boundaries are approximately 4° to 9° N. and 3° to 11° E. cutaneous leishmaniasis has not yet been proved to

# CASE 3



Photomicrograph of smear from ulcerated nodule showing *Leishmania tropica*  $\times 870$



## CASE 6

Extensive ulceration of the right breast. Numerous fusiform bacilli in the smears as well as leishmania.



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occur though many suspicious lesions have been examined at the Medical Research Institute over a number of years. It is interesting to note that in the French Cameroons twenty cases were confirmed in 1935 and 1936 by HERVÉ (1937). He states that they occurred in the southern part of the territory which adjoins the eastern boundary of Southern Nigeria.

His observations should stimulate further search for the parasite in our Southern Provinces.

#### SUMMARY

The occurrence of cutaneous leishmaniasis in Nigeria is noted. Ten cases affecting both Africans and Europeans were confirmed by finding the parasite. Eight occurred in the northern part of the territory and two came from Maradi in French Niger Colony.

#### REFERENCES

- CRAIG C. F. & FAUST E. C. (1937). *Clinical Parasitology* p. 128. Philadelphia: Lea & Febiger.
- HERVÉ (1937). *Ann. Méd. Pharm. colon.*, 35, 1928 (abstracted in *Trop. Dis. Bull.*, 35, 1938 p. 877).
- MANSON-BAHR, P. H. (1940). *Manson's Tropical Diseases* 11th edn. p. 197. London: Cassell & Co.
- MCCULLOCH, W. E. (1928). *IV Afr. med. J.* 2 (1) 98.
- (1930). Annual Report on the Pathological Laboratory Kaduna, *Annual Medical and Sanitary Report Nigeria, for the year 1929* Appendix p. 65.
- SMITH, E. C. (1932). *An Atlas of Skin Diseases in the Tropics* p. 15. London: John Bale.
- (1939). *An Introduction to Pathology and Bacteriology for Medical Students in the Tropics*, p. 173. London: John Bale.



## ABDOMINAL PAIN IN THE DIAGNOSIS OF EARLY KALA-AZAR.

BY

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COLE, COSGROVE and ROBINSON (1942) have recorded a very interesting series of cases of kala azar in a battalion of the King's African Rifles. In their report they state since all were under medical care from the outset a more accurate picture of the disease can be obtained than would be possible from the study of sporadic cases entering civil hospitals. This is very true for unless a number of cases can be under observation from the very beginning of their illness and later followed up over a long period (which is not possible in civil hospital practice as a rule—especially the "following up" part) certain inconsistencies in the usual description of kala azar are bound to be missed. What particularly interests me is the report of abdominal pain in fourteen cases of the series. COLE and his fellow workers quote, "five of them vomiting". The literature I have searched so far (including among other works, the 11th edition of *Manson's Tropical Diseases* (1940), and even NAPIER'S *Kala Azar* (1927)) has contained no reference to this interesting and to my mind, diagnostic, symptom of early or insidious kala-azar—especially in known endemic areas, such as the District wherein I have been resident for many years. I may say that this early symptom has been the only evidence of what has later turned out to be definite kala azar in some hundreds of cases.

as regards treatment and choice of drugs, COLZ and his colleagues seem to have been singularly unfortunate. The exhaustion of all Bayer supplies of neo-stibosan, solustibosan so widely favoured pre War has been a great blow to all engaged in anti kala-azar work. I have had to resort to the less favoured urea stibamine, neo-stibene, or stiburea. In my notes on kala-azar published recently loc. cit., I made an appeal for a British foolproof equivalent of the German neo-stibosan—the best drug I had ever used before the War. Recent samples of the Glaxo Laboratories product stibatin promise to be the (British) answer to my plea. It is a pentavalent antimony solution, and capable of either intramuscular or intravenous administration. The makers claim this substance to be as active and as free from toxicity as the German product. I hope to be able to endorse these claims after the personal trial of stibatin (at present proceeding) is completed.

The following case notes will I think, suffice to illustrate the significance of the early symptom of abdominal pain in kala-azar —

*Case — Shishala — Coole girl aged 17*

Had severe epigastric pain in November 1942. Attended out-patient's clinic for some days and was discharged. Returned on 1st January 1943 because of increase of pain with diarrhoea. Admitted to hospital and kept under observation. Routine aldehyde and Chopra tests negative on admission. There was severe vomiting after food with occasional diarrhoea and complaint of indigestion and great weakness. The patient had become very thin since November 1942. Appetite good and tongue clean, but patient "afraid to eat." Nothing else found on careful examination. My assistant being new first tried gastric palliative treatment with no success. I advised a further blood test 10 days after admission. This time Chopra's test was + and the aldehyde ++ not very definitely conclusive. However urea stibamine was ordered forthwith in view of the typical case history reported. After the third injection of 0.15 grammes the severe pain ceased and also the vomiting. Weakness was however extreme and no solids could be retained. Emaciation progressed. The diarrhoea had ceased. On 28th January 1943 a cough developed—a mild bronchitis. There was no temperature throughout the illness. Urea stibamine was temporarily withheld owing to the bronchitis. On 1st February—only 21 days after admission—dyspnoea occurred and the patient died a few minutes later.

Space does not permit of the recording here of other cases which ended more happily. Indeed, it is hardly necessary as the history is so similar. With reference to the symptomatology of kala-azar MANTON BAKER (1942) says on page 184 of the latest edition of his textbook —

"The onset of the disease may be either gradual or sudden. In the former instance it cannot be diagnosed at all on clinical grounds, etc.

By long and careful observation I believe I am in a position to state definitely that the recognition of the significance of the symptom discussed (even though it may be seen only in 2 or 3 per cent. of cases) provides a clue to the diagnosis on clinical grounds of those gradual (or early) cases referred to by MANTON BAKER. It must be clearly appreciated that it is not my claim that abdominal pain *per se* is a definite sign of kala-azar in all cases. There are many typical or acute cases of kala-azar which give no history of abdominal pain at all. To my mind the symptom, as I have described it, of abdominal

pain some diarrhoea and a suspicious family history all justify—in the absence of proof of any sort to the contrary—a diagnosis of early or insidious kala-azar, especially in definitely epidemic or endemic areas. It should be known and borne in mind by all workers in such areas and I consider that the symptom occurs often enough to warrant its inclusion in the future in the ordinary text-books of tropical medicine among the *lesser* known early symptoms of the disease.

To conclude, it may be observed that a reference to the intestinal or gastric pathology of kala azar would suggest that the cause of this abdominal pain is no doubt due to excessive congestion or even actual blocking of the capillaries of the gastric mucosa with leishmania. In cerebral malaria the capillaries become blocked with resultant irritation of the brain and severe headache, and the same occurs in cerebral human trypanosomiasis, so the kala-azar analogy of the cause of gastric pain is surely not unreasonable. Finally there is a similar explanation in my opinion, for the severe backache which I have often observed in cases of malarial nephritis which so commonly affects children in this District of Mangaldai and elsewhere in Assam. It would be gratifying to have some other colleague's corroboration of my observations in connection with this interesting symptom of early abdominal pain.

#### SUMMARY

- 1 Abdominal pain is often diagnostic of early kala-azar
- 2 This symptom, in my experience, occurs in endemic areas in 2 or 3 per cent. of all kala azar cases, and this is often enough, in my opinion, to warrant its addition in future to the general description of the *early* symptoms in text books.
- 3 A family history must *always* be taken and is of great value, in certain cases, for arriving at a correct and early diagnosis even with negative laboratory findings.
- 4 Stibatin a new British product of pentavalent antimony in solution, promises to equal former Bayer kala-azar remedies

#### REFERENCES.

- BURKE, E. (1943) Notes on the control of kala azar on tea estates *Indian med. Gaz.*, 78 20 22 25
- COLL, A. C. E. COSGROVE, P. C. & ROBINSON M. B. (1942) A preliminary report of an outbreak of kala-azar in a battalion of the King's African Rifles *Trans. R. Soc. trop. Med. Hyg.* 36 25 28 30 32.
- MANSON-BAHR, P. H. (1940) *Manson's Tropical Diseases* 11th ed. p 184 London Cassell & Co. Ltd
- NAPIER, L. E. (1927) *Kala-azar* London Oxford University Press



## AN UNUSUAL CASE OF KALA-AZAR SUCCESSFULLY TREATED WITH STILBAMIDINE

BY

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*H Q Middle East Force*

Corporal S P aged 25 of the Greek Army, was admitted to hospital on 28th July 1942, with a three months' history of lassitude, fever, and loss of weight.

He was born on the Greek island of Ikaria. In 1939 he left his home for Samos, to carry out his compulsory military training. 1940 found him in Thrace from whence he went to Albania, serving in the Greco-Italian War. In June 1941, he returned to Ikaria. He left as a fugitive in early September, 1941. It is reasonably certain therefore, that infection occurred in Ikaria.

**On admission.** Thin emaciated, dark young man with hollow cheeks dry hair receding on his forehead protuberant abdomen. He was pale but cheerful. Weight 114 lb. Urine N.A.D. Teeth throat, and tongue showed no abnormality. No enlarged glands were palpable in the axillae, groins or neck. The cardiovascular and central nervous systems showed no abnormality. A pleural rub was heard at the right base posteriorly. No free fluid was detected in the abdominal cavity. The spleen was not palpable. The liver was palpable 3 inches below the right costal margin. The edge was hard, but not tender. Temperature 100° F pulse, + respirations normal.

Ten days later there was no clinical change except that there seemed to be irregular consolidation of the right base. A 4-hourly temperature pulse and respiration chart showed a remittent pyrexia fluctuating between 98.6° and 103° F. The pulse was normal in relation to the temperature and the respiration rate was not raised. The following investigations had been done to date. Repeated blood smears for malaria parasites and spirochaetes were negative. Six stools for amoebae and cysts and *Bilharzia mansoni* were negative. Three blood cultures were sterile. Three serological examinations for typhoid,

\* I am extremely grateful to Professor ADLER for his invaluable guidance in the management of this case.



paratyphoid A & B abortus, melitensis and typhus fevers were negative. Haemoglobin, 82 per cent. Red blood cells, 3,900 000 White blood cells, 5,200 Polymorphonuclear 60 per cent. lymphocytes, 38 per cent mononuclears, 1 per cent., eosinophiles, 1 per cent. No primitive white cells were seen. Blood pressure 100/55 Straight X ray of chest showed Right diaphragm raised up to the fourth interspace. Small area of consolidation above diaphragm. Left chest normal. No evidence of tuberculosis."

### Treatment

One gram of emetine daily for 4 days, was given. Stools examined on these days were negative for amoebae and cysts. After the second injection he complained of pain and tenderness in the liver region, and this disappeared after the fourth grain of emetine. There was no appreciable diminution in the size of the liver and the fever continued remittent. About this time it was observed that there was a tendency—not marked—for the temperature chart to show a double daily rise. Also noteworthy especially in view of the prolonged pyrexia, were the patient's general feeling of well being and his excellent appetite. The formol-gel reaction was strongly and instantly positive. Sternal puncture was done and the marrow juice sown on four tubes of Locke blood agar and in addition 2 c.c. of venous blood was sown on a fifth tube. In all the tubes flagellates of *Leishmania* were found after 9 days.

Two courses of stilbamidine were given with an interval of 17 days between the two courses. In the first course 23 injections were given. Starting with 50 mg. daily the dose was increased to 100 mg. daily until a total of 2 grammes had been given. In the second course fifteen injections were given. Commencing with 50 mg. daily the dose was increased to 100 and finally to 150 mg. daily until a total of 2 grammes had been given. In both courses together 4 grammes were given. Relevant investigations, including the serum proteins, done before, during, and after are tabulated below.

	Formol-gel reaction	Total Protein proteins g.	Albumin globulins %	Globulin globulins %	A/G Glob ratio	Haemoglobin	Total R.B.C.	Total W.B.C.	Polys %	Lymphs	Blood sedimentation rate in 1 hour	Weight Lib
Normal	—	7.80	4.50	3.70	1.7/1	86	3,500,000	6,000	70	25	2.16	
Before treatment	Instantly positive	10.60	2.80	7.92	22/7	86	3,330,000	2,500	48	54	1.80	112
Between courses	Instantly positive	13.00	1.20	11.79	11/1	96	3,710,000	4,440	73	19	1.40	117
After treatment	Positive after 30 secs	10.60	3.30	7.31	47/1	75	4,140,000	8,800	80	49	1.00	125
Four months after treatment	—	8.72	3.50	5.22	1.4/1	83	4,000,000	2,300	73	21	.90	127

Stilbamidine (M & B 744) is 4,4'-diaminodiphenylstilbene dihydrochloride.

At the end of the first course the patient felt well had gained 5 lb in weight and his blood picture had improved. The abnormal signs at his right base had gone and this was confirmed by X ray, which showed no abnormality with both diaphragms moving well. His liver was smaller palpable only 1 inch below the costal margin. His temperature remained down 10 days after the commencement of the course. However in view of the grossly abnormal blood protein figures which persisted (the exceptionally high total protein and the distorted albumin globulin ratio) it was decided to give the second course of stilbamidine.

The drug was supplied in powder form in ampoules each containing 1 gramme. The required quantity was weighed out and placed in a small sterile conical flask. About 2 c.c. of anaesthetic ether was added the night before use and the flask lightly stopped with cotton-wool to allow evaporation overnight. The addition of ether would not have been necessary had the weighing been done under sterile conditions. One hour before administration 20 c.c. of chemically pure sterile water was added to the now dry powder and this was dissolved by carefully rotating the flask. The injection was then given intravenously and slowly. The vein used invariably thrombosed and towards the end of the first course small veins on the backs of the hand had to be used, the injection being given with a hypodermic needle. For this reason the early injections of the second course were given into the more peripheral veins. On four occasions some of the solution penetrated the tissues. The patient complained of immediate pain. However in no case did the pain persist for longer than 2 hours and there was no abscess formation. Adrenalin was ready for use during injections but was never used. Flushing of the face was noticed several times during the second course when 150 mg doses were given. The injections were given 1 hour before the midday meal. The patient remained in bed during the treatment. He was given calcium and vitamin preparations by mouth and a liberal diet rich in carbohydrates.

The serum protein analyses in this case are of interest because of the high globulin albumin ratio after the first course of treatment, figures which are unusually high even for kala azar. Another interesting feature is the fact that at no time during the illness was the spleen palpable.



## ASTHMA PRODUCED BY ASCARIS INFESTATION

BY

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An account of an asthmatic attack that appeared to be directly related to ascaris infestation seems to be sufficiently interesting to merit recording. The case occurred at sea, on board a ship of the Canadian Merchant Navy. The limitations of maritime medicine account for the paucity of laboratory work in connection with the case.

### Case History

J. M., aged 22 negro native of Montserrat, British West Indies, was seen on the night of 12th April, 1942. At that time he was sitting on the deck outside the sick bay his hands pressed tightly to the deck so as to bring the accessory respiratory muscles into play. He was extremely cyanosed, sweating, with cold extremities and feeble pulse. He was also extremely nervous and alarmed at what was to him a novel experience and was convinced that he was going to die. Whilst I was preparing an adrenalin injection the patient vomited some frothy very bile-stained material, in which were moving three live ascaris worms. Unfortunately these were thrown overboard before their sex could be determined. Almost immediately after vomiting the patient experienced great relief and although I gave him the adrenalin injection, I think that the symptoms might have cleared up without any medication whatever.

There was no family history of asthma or any other allergic disease. The patient had lived in Montserrat all his life with the exception of one trip to St. Kitts and the present voyage, in which he had gone as first Officer, Canadian Merchant Navy. He was positive that this was the first asthmatic attack that he had ever had in his life and gave no history of hay fever or urticaria. He was the victim of an and unknown nature of the malady that had caused him to be so terrified when first seen.

\* I have to thank Dr. H. H. BAYLEY of St. Michael, Barbados for the information performed in connection with the above investigation and also for the ascaris antigen.

The patient was treated next day with hexylresorcinol crystals 1 gramme, combined with pre and post vermifuge purgation with magnesium sulphate. All stools passed by the patient during the ensuing week were carefully searched for worms: none was found. A second treatment with hexylresorcinol likewise yielded negative results. Stool specimens, examined ashore in Barbados, were negative for ova or protozoa. Skin tests—both scratch and intradermal—using an aqueous extract of preserved *Ascaris* were positive.

During the rest of the time that the patient was under my observation he never again had an asthmatic attack nor did he show any other allergic manifestation. Unfortunately about 1 month later he lost his life when the ship on which we were serving was torpedoed by the enemy.

### DISCUSSION

Asthma produced by adult *Ascaris* and their emanations is described by HANSEN (1929), BRAY (1936) CRAIG and FAUST (1940). HANSEN (1929) describes cases in which the asthma persisted as long as the patients were infested with worms, but disappeared the moment they were removed. BACHMAN has stated, however, that persons—as shown by skin tests—may retain sensitivity to the ascaris antigen long after the worms have been removed and also that some persons may acquire a sensitivity as a result of contact with infected individuals.

In this case it appears that the patient was sensitive to ascaris-antigen but showed no clinical manifestation of his sensitivity until an attack of asthma was precipitated by the migration of three worms from the small intestine into the stomach. It seems very likely that these three worms alone were the cause of the man's trouble, as it cleared up immediately they were expelled. It also seems likely that the three worms vomited up represented the sum total of the patient's ascaris infestation, as no further evidence of infestation was ever discovered.

### SUMMARY

1. An attack of asthma, probably caused by migrating adult *Ascaris* is described.
2. Similar manifestations described by other observers are discussed.

### REFERENCES

- BACHMAN, G. Personal communication. Quoted by CRAIG and FAUST.  
 BRAY, G. W. (1936). *Recent Advances in Allergy*. 3rd Edition, page 497. London: J. & A. Churchill, Ltd.  
 CRAIG, C. F. & FAUST, E. C. (1940). *Clinical Parasitology*. 2nd Edition, page 299. Philadelphia: Lea & Febiger.  
 HANSEN, (1929). *Practitioner* 122, 52. (Quoted by BRAY.)

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